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INFECTION IN THE NEWBORN BABY*

BY

ALAN MONCRIEFF, C.B.E., M.D., F.R.C.P.

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It is a great honour to give the Charles West Lecture, and I appreciate it all the more because this is the centenary year of the famous hospital he founded in Great Ormond Street. I am also happy that on the first occasion this lecture is given by a London paediatrician it has fallen to the lot of one who also had the privilege of serving the Middlesex Hospital, where West was a lecturer on midwifery in the years before he devoted his undivided attention to the sick child. I have chosen the subject of infection in the newborn baby partly because of West's own interest in this subject as an obstetrician and also because I believe it was through this subject, encountered when he was studying in Dublin, that he first became interested in the sick child.

Charles West's Activities

Previous lecturers have given short sketches of Charles West, but this year I beg leave to say a little more by way of introduction. He was a Fellow of this College, Senior Censor, and Harveian Orator. His Fellowship came the same year as he first published his famous book, *Lectures on the Diseases of Infancy and Childhood*, based upon lectures to the students of Middlesex Hospital during the summer of 1847. It is rather surprising that, although officially the lecturer in midwifery, West devoted comparatively little space in his book to diseases of the newborn baby. He writes of "atelektasis"—a form of spelling now discarded—and in recognizing a congenital form he stresses the considerable pressure sometimes required to inflate the lungs. He notes that facial palsy can occur in the newborn baby "from injury received during the passage of the head through the pelvis without any instruments having been employed." West mentions that recovery in a few weeks is the usual story. He also makes the observation in regard to icterus neonatorum that it seems to be common if the child is chilled.

It is, however, in West's comments on "trismus" that we find a clue to his subsequent activities. He uses this term for tetanus neonatorum, but, like Cameron (1929), he recognizes that trismus can be caused by sepsis and that it is not always due to tetanus. In writing of this condition he states that "sixty years ago"—that is, during the closing decades of the eighteenth century—every sixth child born in the Dublin Lying-In Hospital died within a fortnight, and trismus was the cause in 19 out of 20 cases. Efficient ventilating of the hospital was then achieved—so runs West's story—so that by 1833 the mortality had fallen from 1 in 6 to 1 in 58¼, and only 1 in 9 were due to trismus.

The points to be noted here are the appalling mortality among newborn babies, much of which was due to infection, and the reduction of the risk by certain elementary hygienic precautions. The fear of infection among children in hospital was the dominant factor in deciding policy in the early part of the nineteenth century. West was clearly impressed by the seriousness of the problem as he saw it in the lying-in hospital and by the statistical evidence of improvement achieved by certain measures. First he became interested in the sick child, and next in the provision of properly conducted hospital facilities. Hence "Great Ormond Street"; and, as Cameron has put it, "it is to obstetricians that the study of paediatrics owes its birth."

Some Scottish Figures

Charles West gave statistics to illustrate the events in Dublin, which so greatly influenced his life. I must now interpolate some more modern figures to indicate the possible extent of the problem. For this purpose I propose to rely almost entirely on reports from Scotland, because it happens that there are a series of figures available over the last twenty years which illustrate the chief aspects of the subject. Cruickshank (1930), in his study of neonatal death, ascribed this to infective conditions in 238 out of the 800 infants examined *post mortem*. He classified about 15% of the 800 infants as suffering from septicaemia, but thought this approximate and likely to be too low. For the purpose of this lecture Cruickshank's report is important for two things. First, that at least 30% of babies dying in the first month of life were dying of infection; and, secondly, that in only 7 out of the whole 800 was he satisfied that the form of infection could be called "umbilical sepsis." He stresses that nowadays umbilical sepsis is a rare variety of neonatal infection and that local umbilical stump infection is also most unusual. This is an important negative point, for far too many people to-day, doctors and midwives, in my experience, associate the word sepsis when used in reference to the newborn as meaning only umbilical sepsis. It is well that a pathologist from the city where Lister worked should stress the rarity of umbilical sepsis in the post-Lister era.

A real step forward towards recognizing other forms of neonatal infection can be made when this fact is firmly recognized. Confusion perhaps exists because a mild superficial omphalitis is not uncommon after the cord has separated, and it is not unusual in welfare centre work for babies to have a slightly blood-stained discharge, with or without an "umbilical polyp," about the second fortnight of life. This very rarely causes

*The Charles West Lecture delivered at the Royal College of Physicians of London on November 11, 1952.

more than local trouble, and has nothing in common with the devastating umbilical sepsis such as West undoubtedly saw in the lying-in wards a century ago. Cruickshank's figures are almost the same as those of Agnes Macgregor (1946), who, working in Edinburgh, found infection to be a cause of neonatal death in 190 out of 618 infants, or 30.7%. This was the commonest single cause of neonatal death. It was responsible for two out of every three deaths after the third day of life. Both the Glasgow and the Edinburgh figures refer essentially to the period before modern chemotherapy became available, and it is likely that the incidence of infection as a cause of death in the newborn is less to-day.

Sepsis must, however, be recognized if it is to be treated efficiently, and unfortunately there is evidence that the condition is often overlooked. A further report from Scotland makes this point clear (Department of Health for Scotland, 1947). Discussing in general terms the neonatal mortality in Scotland, the report notes "that in a considerable proportion of deaths the cause is erroneously certified." Figures given for the period 1939–43 at the Royal Maternity Hospital, Glasgow, show that in the first three days of life deaths due to infection proved *post mortem* accounted for 15.4% of the total deaths, whereas on the clinical diagnosis only 3.5% were recorded as due to infection. For the first week the figures were 20.5 and 8.5% respectively, and over the whole of the first month of life 36.4 and 17.6%. It is noteworthy that it is in the early days of life that the clinical diagnosis is more often erroneous. Figures from four municipal hospitals in the same city over the same period revealed a similar discrepancy. On the whole the figures in Scotland show lower figures for smaller hospitals and hospitals taking fewer emergency cases.

The Common Cold

What perhaps is most striking in the Scottish report is that it makes no mention of what is in my opinion a common cause of trouble just because it is so common—namely, the common cold. It is, of course, probable that when this kills, as it may quite often do in the newborn, and especially in the premature infant, it kills by bronchopneumonia or by gastro-enteritis. What seems clear is that it is often missed as a clinical entity. It is interesting to note that in another report covering the whole subject of neonatal mortality and morbidity (Ministry of Health, 1949) the section on infection in the newborn also fails to mention the common cold, and as one of those who helped to draw up this report I must clearly accept some responsibility for this omission.

Why is the common cold not recognized in the newborn? It is because the pattern of disease in infancy, to use Spence's (1941) term, is different from the pattern in adults and so variable as to give little direct help in diagnosis, which has largely to be on circumstantial evidence.

Consider the clinical features of a small baby with a cold. Lying horizontally in bed, he seldom sneezes, and such excess secretion as is present from the nasal mucous membrane passes down the back of the throat. Obstruction of the nose may occur from time to time, leading in the early days of life to breathing difficulties, often quite wrongly attributed to "asphyxia neonatorum." The obstruction also leads to great difficulty over feeding, because the infant cannot suck properly. The result of this may often be engorgement of the breasts in the mother and a failure of lactation—or the baby is weaned because he will not take the breast. The diagnosis of intracranial haemorrhage may be made at this point. Sometimes, but in my experience, rarely, some degree of snuffles and anterior nasal discharge occur, often leading to a suspicion of syphilis and delay while this is excluded. By now the infant may have begun to vomit or have green stools as a manifestation of his parenteral infection.

Alternatively, infection may have spread down the respiratory tract and signs of involvement of the finer bronchi and alveoli of the lungs appear. Whether or not the primary infection of the nose was a virus, there is by now secondary invasion—staphylococcal or by one of the Gram-negative group. All this may happen with surprising rapidity, and death may occur within a few days of the onset, again without any suspicion that the original infection was essentially of the upper respiratory tract. Again and again with this picture it is possible to track the infection back to the baby's contact with an adult who has a nasal infection. The mother herself may have a chronic sinus infection (as in one of my patients), or the trouble may have come from one of the nursing staff (in one instance a night nurse in a nursing-home where at that period the matron did not "hold" with masks). Things are perhaps a little better than they were, because the use of masks is more widespread, but so long as the cold is largely unrecognized in the baby for what it is the menace will continue.

Difficulties in Diagnosis of Infection

Two fundamental difficulties seem to exist in the failure to recognize neonatal infection for what it is. First, there is a popular tradition that babies do not "catch" infections. This is of course based upon the fact that the common infectious fevers are uncommon in the early months of life. This is presumably due to temporary passive immunity transferred from the mother across the placenta. It can occur only if the mother herself is immune. Hence although the infectious fevers are rare in early infancy they can all occur. I have myself seen chicken-pox at 3 weeks, and I have performed an emergency tracheotomy for laryngeal diphtheria at 10 weeks. I have knowledge of whooping-cough more or less from birth, the mother herself suffering from the disease at the time of birth; and the literature contains records of unusual cases of the other specific fevers, when the mother has no immunity to pass on. In the case of other infections—those caused by staphylococci, pneumococci, for example—or the common cold, maternal immunity is not likely to be very solid, and therefore the newborn baby is not protected against these common infections. I shall refer later to the larger question of transferred immunity; here it is sufficient to emphasize that the baby is unlikely to have immunity unless the mother possesses it, and that maternal immunity to the infections just mentioned is never permanent.

The second reason for difficulty in accepting a diagnosis of infection in the neonatal period is concerned with the temperature chart and what is meant by fever. All newborn babies, and more especially prematurely born infants, tend to have a basic temperature at first below the commonly accepted adult levels. Thus if 99° F. (37.2° C.) is accepted as an average rectal temperature reading in the adult (or older child), a corresponding figure for the early days of life is nearer 97° F. (36.1° C.) and sometimes lower. This slowly rises as the infant's metabolism and heat-regulating mechanism get adjusted to post-natal life, but the "adult" level is often not reached for 10 or 14 days. A rise of 2° F. (1.1° C.) during the period will still only bring the baby to the "adult" level. If the temperature of the baby has not been recorded until some unusual symptoms and signs appear it is quite easy, after a reading of say 99 to 99.5° F. (37.2 to 37.5° C.) has been recorded by a rectal thermometer, to assume that no "fever" is present, and hence infection is an unlikely explanation for the infant's malady. Yet in fact the rise in temperature is more nearly equivalent to a reading of 101° F. (38.3° C.) or more in the adult, and from the point of view of a rise in temperature is quite clearly fever in the usual sense of the word. These points are illustrated in Figs. 1 and 2, and I have added for the sake of completeness a chart (Fig. 3) to show how sometimes overwhelming infection in the newborn actually causes a subnormal temperature before death. Regular daily temperature-recording should be carried out for all babies (as for all mothers) in the newborn period, so that an early rise can be detected.

If these two fundamental difficulties are kept in mind the diagnosis of sepsis in the newborn becomes easier, but it still remains difficult. Spence (1941) makes a valuable generalization: "A newborn infant who becomes abnormally

drowsy and refuses its feeds and is not suffering from cerebral haemorrhage should be suspected of an acute neonatal infection." I would go a little further and state that *any* disturbance in the newborn baby after the first few days of life should be regarded as due to infection until proved otherwise. Let me here record a personal failure to observe this rule.

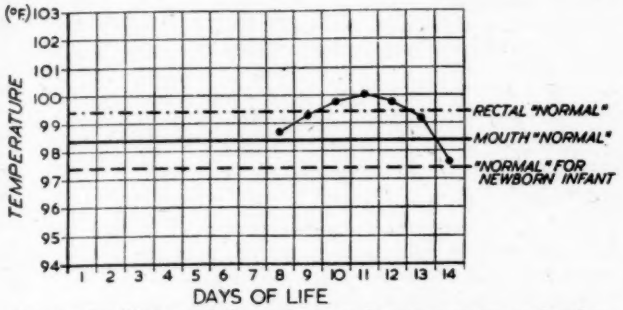

FIG. 1.—To illustrate fallacy of measuring temperature only when infant becomes ill—for example, on the eighth day. By "adult" or "normal" standards no rise is detectable and fever may be declared absent (cf. Fig. 2).

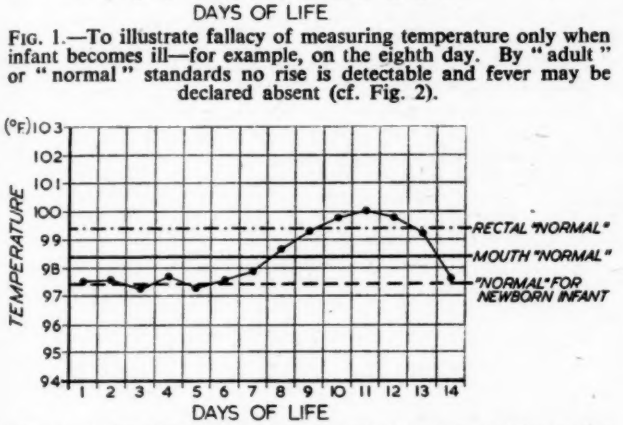

FIG. 2.—When temperature is measured daily from birth the rise on the eighth and successive days is clearly visible and there is no doubt about the febrile state.

A baby girl was admitted to my ward at the age of 5 days, having been seen by a colleague in a nursing-home. She was regarded as a case of haemorrhagic disease of the newborn, for on the third day she had begun to vomit small amounts of bright blood followed by brownish vomits for several days. There was a story that shortly after a normal labour she had regurgitated a little brownish mucus. Meconium had been normally passed. There was no melaena. The baby was not seriously ill. The rectal temperature on admission was 97° F. (36.1° C.). Clinical examination showed no signs of chest disease. The diagnosis of haemorrhagic disease was accepted and vitamin K was given for several days. Four days after admission she had a cyanotic attack (subsequently it was learned that two slight similar attacks had occurred before admission). I carefully examined the chest but could find no physical signs. The child was taking feeds well, gaining weight (? due to oedema), and there was no further bleeding. At 10 days the child was vaguely not doing too well. White blood cells were 14,600 per c.mm., with 79% polymorphonuclears. There were still no signs. Then rapid deterioration set in. The temperature was still only 99° F. (37.2° C.) rectal—that is, 2° F. (1.1° C.) up—and for the first time there were signs in the chest: weaker air entry at the left base with crepitations. Puffiness of the face and distension of the abdomen developed. Aureomycin was started, but was much too late. The baby died next day. At necropsy there was a right-sided empyema and multiple lung abscesses suggestive of an inhalational septic pneumonia. *Staphylococcus aureus* (coagulase-positive) was grown from the empyema.

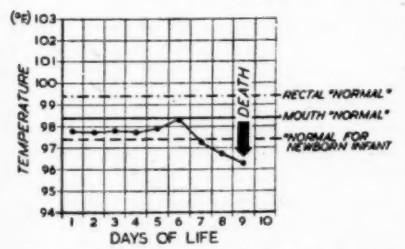

FIG. 3.—Effect of overwhelming infection producing paradoxical fall in temperature before death.

Here, then, was a fatal case of neonatal sepsis in which the essential diagnosis was missed despite all the resources of a modern hospital and the expert supervision of what have been termed "high priced" clinicians. It serves to emphasize the essential difficulties of the subject.

I now would like to turn to certain special types of infection in the newborn, and I shall use the classification of infection acquired before, during, and after birth.

Infections Acquired Before Birth

Of infections acquired before birth *congenital syphilis* is the best known and most studied, and, beyond stating categorically that it is a completely preventable disease if routine antenatal serological tests are conscientiously done and treatment is instituted, I will omit further reference. *Tuberculosis* may occur in a congenital form.

In the case of a baby born at full term and weighing 7 lb. (3.2 kg.) the young mother had developed a pleural effusion at the sixth month of pregnancy, and although this was not proved to be tuberculous at the time there was clear evidence three years later of healed lesions in her lungs. The placenta was said to be normal to the naked eye. The baby became ill on the fifth day of life and died at 1 month of age. Post-mortem examination (by Professor R. W. Scarff) showed advanced miliary tuberculosis with the most marked changes in the region of the portal fissure. The lungs and spleen were also invaded by miliary tuberculosis. There is little doubt that this was a transplacental transmission of tubercle bacilli. The point of interest is the mild nature of the mother's illness.

Infection by *Bact. coli* has been recorded many times. I have records of a baby dying in a nursing-home on the 10th day of life with what I can only call a fulminating pyelitis with *Bact. coli* in the urine—before the days of chemotherapy. The mother had suffered from pyelitis intermittently during pregnancy, with a flare-up in the puerperium. I also recall a patient described to me by Professor W. C. W. Nixon in whom meningitis due to *Bact. coli* caused death about the 4th day of life: the mother also had suffered from pyelitis during pregnancy. Pneumococci can also pass across the placental barrier. Cruickshank (1930) mentions the case of a mother who had pneumonia just before her delivery. The baby died on the 3rd day of life and was found to have advanced lobar pneumonia with grey hepatization.

Turning from bacterial infections, we reach some fascinating and speculative problems. *Congenital malaria* has been much debated by experts and is well discussed in a monograph by the late Professor A. Eckstein (1946). He and Nixon also described undoubted cases occurring in newborn babies in a hospital where malaria was not endemic (Eckstein and Nixon, 1946). Jones and Brown (1924) described the case of a mother who had been travelling on the Continent: her baby, born in England, developed malaria on the 16th day of life. I have no doubt, from reading much of the literature, that the disease can be transmitted from the mother. Experts disagree about whether or not the parasite can pass across an intact and healthy placenta, and suggest that this can happen only when accidental tears occur. Perhaps there is a similar mechanism to what happens in rhesus factor incompatibility when the first and sensitizing baby's blood mingles with the mother's at the time of separation of the placenta. Many problems are concerned with this question of malaria in early life. Does it cause death *in utero*? Would it be justifiable to carry out malaria prophylaxis during pregnancy? Is congenital malaria the cause of a high infant mortality rate in endemic areas? Is there in babies born of infected mothers a "latent" malaria, with symptoms which mimic meningitis, causing anaemia, digestive disorders, coma, and convulsions? My experiences in two brief visits to East Africa suggest that the whole problem requires very careful thought. Malarial infection in early life is valuable, so it is said, for producing "immunity" or "premunity" among the adult African population. The children's physician, perhaps short-sightedly, ventures to ask about the price paid in infant mortality.

Toxoplasmosis may be mentioned next, as the infecting organisms are also protozoa. There is no question here about the congenital form with a high mortality rate in early infancy and the development of symptoms in survivors within a few weeks of birth. Again the question of the placenta arises. Few studies have been made, but it is reported in one instance to have been abnormal in colour and appearance. There have been numerous papers on the whole subject in recent times, and the problems are well reviewed by Wyllie, Fisher, and Cathie (1950). This communication also refers to published cases on newborn babies of infection by the fungus *Torula histolytica*.

Virus Infections

Next we come to a large group of virus infections about which it is possible to mention only a few special points. (I am indebted to my colleagues Dr. Martin Bodian and Dr. J. A. Dudgeon for particular help in this section.) Here, as probably with many antenatal infections, foetal mortality is high, and when the infection occurs in the first trimester of pregnancy congenital malformations may result, as in the well-known rubella syndrome.

The effects on the unborn child of *variola* and of *vaccinia* in the mother have been reviewed by Lynch (1932), and MacArthur (1952) has recounted experiences in Lanarkshire following vaccination as a result of a smallpox outbreak. There appear to be dangers for the unborn babe, and, according to Lynch, little immunity is transmitted by vaccination. (This is not in accord with the findings of Marsden and Greenfield, 1934.)

Herpes in the mother may be associated with the early development of encephalitis after birth (Quilligan and Wilson, 1951; Wildi, 1951), and it is tempting to postulate intrauterine infection. Zuelzer and Stulberg (1952) have reported examples of herpes with hepatitis in newborn infants, and in one of these there was certainly the possibility of transplacental transmission of the virus.

Poliomyelitis in the mother may not necessarily infect the baby, although abortion may occur (Baker and Baker, 1947). There are many dramatic records of caesarean section in a dying mother or even after death resulting in a normal infant (Stokes, 1946; Simmons and Ellis, 1949). On the other hand, there are also records in which the infant had poliomyelitis at birth (Aycock and Ingalls, 1946).

A rare but fascinating virus infection is that described nowadays as "cytomegalic inclusion disease." This is particularly important because it can be mistaken for haemolytic disease of the newborn, and the jaundice which occurs raises points of interest in relation to virus infection and hepatitis (see below). Cappell and McFarlane (1947) reported giant cells with cytoplasmic and intranuclear inclusion bodies in the organs of two infants alleged to have died of haemolytic disease although there was no evidence of blood-group incompatibility. They concluded that the lesions were identical with those found in the salivary gland virus disease of rodents and monkeys. France (1951) has reviewed the clinical picture and pathological findings, and by the kindness of my colleagues Dr. G. Newns and Dr. M. Bodian I am able to report the case of a child who died with a clinical diagnosis of neonatal hepatitis and was found at necropsy to have suffered from cytomegalic inclusion disease.

The mother suffered from an attack of "influenza" at the fifth month of pregnancy. The child was very premature by weight—3¼ lb. (1.6 kg.)—and on the second day of life showed slight jaundice which lasted only for 24 hours. Subsequently he developed pitting oedema of feet, legs, and abdomen, and when the oedema subsided at the age of 26 days the jaundice again became apparent. The stools contained bilirubin on two occasions. He made no real progress and developed a staphylococcal upper and lower respiratory infection, dying at the age of 11 weeks.

At necropsy there was pulmonary emphysema and collapse. The liver was slightly enlarged and olive-green, and the bile ducts were normal and patent. Histological examination showed the replacement of portal areas in the liver by granulation tissue and the almost complete disappearance of bile-duct epithelium. There was a retention of bile in canaliculi and hepatic cells, and many of the liver cells, principally in the peripheral parts of the lobule, were larger than normal, and some were multinucleate. The most interesting findings were in the submaxillary glands, which contained numerous intranuclear and intracytoplasmic inclusions in the epithelium of smaller ducts. A few scattered foci of cytoplasmic inclusions were also found in the convoluted tubules of the kidneys.

It is therefore concluded that this child suffered from cytomegalic inclusion disease which seemed to have affected epithelial cells in various situations, and it is suggested that the disappearance of the biliary epithelium was the result of this disease, although no inclusions were, in fact, found in the bile ducts or in the liver cells. This would appear to have been a case of hepatitis and cholangitis due to cytomegalic inclusion disease.

Hepatitis

It seems likely from the early development of signs and symptoms that the "salivary gland virus" is transmitted from the mother. This also seems possible with the viruses concerned with hepatitis. Here we reach a complicated and very important subject. First let me describe some clinical problems in this field.

A trained nurse "caught" what was called infective hepatitis, presumably the "epidemic virus" type, in 1944. She had a moderate attack and recovered completely. She married, and in 1949 gave birth to a baby boy who was quite severely jaundiced for some time after birth but eventually recovered, although left with an enlarged firm liver which is almost certainly cirrhotic. Two years after the birth of the first child another boy was born who also became jaundiced, and died. Necropsy showed a classical picture of hepatitis.

Is there any connexion between the mother's jaundice and the children's condition? Could she have the virus still latent in the blood? It is held that the virus of epidemic jaundice is in the blood only at the time of the illness, and therefore unless the mother had the disease at the end of the pregnancy the baby would not be likely to be affected. Here is another case record:

A fifth baby was born at term to a rather feckless mother who was known to have had a positive Wassermann reaction and a positive Kahn reaction during pregnancy. The mother had an injection of penicillin at the sixth month and two more during the eighth month of pregnancy, and then defaulted. She had never been jaundiced, nor had any of the other four children. The baby had had no injections. (Incidentally, there never was any serological, clinical, or pathological evidence of syphilitic infection in the baby.) On the fourth day slight jaundice was seen which faded, and the stools were said to be pale. On the tenth day of life the jaundice deepened, the stools were usually pale, and the urine contained bile. The jaundice deepened further and the liver enlarged. Forty-eight days after this baby's admission the nurse who had been mainly responsible for his care developed what appeared to be a classical attack of infective hepatitis, and 16 days later—that is, 64 days after the first contact—a second nurse who had helped with the baby also developed jaundice. Both the nurses recovered after a mild attack. There had been no cases of infective hepatitis among the nurses for about a year and no more cases until six months after this curious episode. Unfortunately the story does not end here. Laparotomy undertaken to eliminate the possibility of obstruction of the bile ducts revealed an enlarged liver which showed in a biopsy the appearances of a biliary cirrhosis secondary to obstruction. The bile ducts and the gall-bladder could not be traced. The baby lived for several months and then died. At necropsy a blind end was found for the hepatic duct and no common duct. The histological appearances were not those of hepatitis.

It is still possible here that some infection from the mother played a part. In a discussion on this subject in the U.S.A. (Stokes *et al.*, 1951) the clinical resemblance between hepatitis in the newborn and atresia of the bile passages was stressed, and it was also mentioned that the histology was confusing. I am not suggesting that in the present case an error has been made: the anatomical findings leave no doubt about the atresia. It is possible, however, for hepatitis to be followed by fibrous-tissue repair sufficiently marked to cause confusion with the appearances in biliary cirrhosis due to obstruction.

A baby was admitted at the age of 5 weeks for jaundice which had started between the second and fifth days of life. The stools

became pale and the urine darkened. For various reasons the condition was regarded as hepatitis. The jaundice continued and the liver enlarged and became firm. Laparotomy revealed the absence of a gall-bladder or bile ducts. Some fibrous tissue lying round the hepatic artery was thought possibly to represent the remains of bile ducts. A portion of liver taken for biopsy showed, however, the picture of active hepato-cellular necrosis and post-necrotic regeneration together with reactive portal fibrosis. The picture was, according to Dr. Bodian, most complex and certainly not that found usually in atresia of the bile ducts.

These cases are of importance when it is remembered that to-day most pregnant women in this country have at least one needle inserted into a vein during the antenatal period, and the opportunity for the introduction of the virus of "serum hepatitis" is there. There is evidence that virus can cross the placenta. In the American discussion mentioned above (Stokes *et al.*, 1951) it was suggested that perhaps yet a third virus was involved and not that of serum hepatitis or of epidemic hepatitis. There was doubt, however, that hepatitis of viral origin can occur in the newborn.

Inhalation of Infected Material

So far the intrauterine infections mentioned have all been blood-borne to the foetus. There is also the possibility of inhalation of infected material.

In the early days of my work in the department for the newborn at the British Postgraduate Hospital the late Professor E. H. Kettle called my attention to a post-mortem examination of a stillborn full-time baby with changes in the left lower lobe very similar to those of pulmonary fibrosis in later childhood, of the type that often proceeds to bronchiectasis. He suggested that the changes were the result of an acute inflammatory process which had occurred three to four months before birth. Examination of the mother's records showed that she had been kept in bed for a few weeks just at this period for a uterine haemorrhage. It is tempting to suggest that partial separation of the placenta had been responsible for initiating inspiratory efforts on the part of the baby.

A recent study by White (1952) of 360 infants, either stillborn or dying during the neonatal period, included 69 infants (29 stillborn) who had aspirated appreciable quantities of particulate amniotic debris, and 39 other infants who showed formation of "hyaline membrane." Associated pneumonia was present in 29 and 12 infants respectively in these two groups. The evidence seems clear that the agent responsible is aspirated with the amniotic contents, possibly breakdown tissue products, the result of premature devitalization of parts of the placenta and foetal membranes. I have always felt that blood may be an irritant in the lungs provoking an inflammatory response, as it does, for example, in the peritoneal cavity in later life. Dr. White also found in a minority of cases of the severest degree, usually associated with prolonged rupture of the membranes, that bacteria could be demonstrated.

Infections Acquired During Birth

Infection during birth is so well recognized that it can be briefly dismissed. Inhalation again plays an important part. It is essential in the management of the newborn baby to carry out a gentle toilet of the mouth and nasopharynx, if possible before the first breath. Infection of the eye at the time of birth is illustrated by gonococcal ophthalmia, and although this has become rare in this country and is now so easily treated that many centres have given up the prophylactic use of silver preparations, the problem of the "sticky eye" still remains numerically one of the most troublesome in the neonatal period. Just as gonococcal ophthalmia has been known to lead to generalized infection on rare occasions, as shown by the development of a gonococcal arthritis, so ophthalmia due to other organisms is important not because of the mild and easily treated local condition, but because the eye may be a portal of entry for generalized "sepsis neonatorum."

It must also be remembered that during or immediately after birth the baby may meet for the first time infective material from other sources than his mother. The historical example of the tuberculous midwife who fatally infected several babies by mouth-to-mouth insufflation is scarcely likely to be repeated to-day, but streptococcal, staphylococcal, and virus infections still lurk in the upper respiratory tract of those attending the newborn, and great personal care is necessary to prevent infection at a period when immunity to such infections is low.

Infections Acquired After Birth

Any discussion of infection after birth ought to deal with the whole problem of immunity, but fortunately it has been well reviewed in recent times by several workers, and especially by Parish (1951). I shall select only a few aspects of the subject for comment.

Passive immunity in humans is probably transmitted almost entirely by the placental route, and certainly not by colostrum, as in certain animals (sheep, goats, cows, horses, and pigs). This species difference is important because it largely rules out arguments from veterinary experience so well reviewed by Lovell (1951). According to this doctrine, in the human subject transferred immunity depends on the layers of placental tissue and on placental permeability. Experiments by Bramball and others, quoted by Parish, throw just a slight doubt on this, however, because it is suggested that antibodies may be present in the amniotic fluid and be swallowed. If it is accepted, however, that the placental route is the more important, there at once arise problems of the size and nature of antibody particulates, whether the process is one of simple filtration or of active secretion or whether, as suggested by Calman and Murray (1951) in a fascinating hypothesis, the mechanism is one of selective passage. They suggest that antibodies in the foetal circulation may result from a breakdown of a complex molecule on the maternal side and the re-forming of antibodies on the foetal side. It is noteworthy that the blood of the foetus may actually have a higher measurable antitoxin level than the blood of the mother. This has also been shown to be true in relation to gamma globulin—for example, by Martin-Du Pan and Moore (1948)—a substance which many regard as the raw material, so to speak, of antibody function.

As regards the development of active immunity, we still do not know in detail how quickly newborn babies can respond by antibody formation when subjected to antigenic stimulation. It may be related to nutritional factors. Calman and Murray make this point when they refer to the amino-acid groupings provided by the mother for antibody formation. It has long been accepted that well-nourished people are better able to withstand infection. Actually experiments have shown that the relationship between nutrition and antibody formation is less close than tradition suggests. Well-nourished soldiers give only slightly better antibody response than others. It is generally felt that interference with amino-acid metabolism is probably more important than any general reduction in diet protein. Pyridoxine deficiency interferes with amino-acid metabolism, and experiments support the idea that antibody response is less in pyridoxine-deficient rats (*Lancet*, 1950). The practical bearing of this lies in the question of whether anything can be done by diet to increase the immunity of the newborn. Is there any special amino-acid grouping which will help? Is there any value, from the immunity standpoint, in enriching human milk with casein hydrolysates in the early weeks for prematurely born infants?

Yet another aspect of neonatal immunity is that of genetics. Here again there is a lack of detailed knowledge.

Recently I had under my care a baby admitted at the age of 5 weeks for neonatal sepsis. This had begun with a stye in the right eye, a septic spot on the right cheek, and a septic thumb while in a nursing-home where he was born. At the age of 4 weeks an infected area appeared on the right leg, and the day before admission his right ear began to discharge. The rest of his life up to the age of 3 months was a losing battle against infection. Despite the use of every modern aid the child never seemed able to overcome the various organisms which invaded him. His cord did not separate until he was a month old, and he had some infection of a persistent urachal sinus. At necropsy the bony parts of his right ear were almost completely destroyed.

An elder child also died from chronic sepsis beginning at the age of 14 days with recurrent boils and cutaneous ulcers. He lived for 15 months, and the comment of a colleague under whose care he was for the last period of his life was that although "there was a good response by the reticulo-endothelial system" this was "not enough to eradicate the infection, even with the help of chemotherapy and fresh blood."

In the case of the second child the white-cell response was adequate throughout, and his response to inoculation with T.A.B. vaccine (to test his antibody response mechanism) was described by Dr. J. C. McFarlane, who kindly did the agglutinations, as "excellent."

Is this family an example of lack of immunity to bacterial invasion genetically determined?

Main Features of Infection After Birth

Coming now to the general picture of infection after birth, I will give a brief description of the main features. First, infection has to gain an entry by way of the mucous membranes of the respiratory tract, the eyes, the skin, the alimentary tract, or the umbilicus. Usually there is some local reaction which may be termed the "primary focus." If the infection is mild and resistance good nothing more may happen except that spread from one infected baby to another may take place—and a favourable outcome in one baby is not necessarily followed in other babies infected from the first. In unfavourable cases generalization of the infection takes place—either a toxaemia or a septicaemia at first, later frequently becoming a pyaemia.

Epidemic diarrhoea of the newborn requires a short separate note. It is fortunately rare, although a constant threat in newborn baby nurseries. It may be of virus origin (Buddingh and Dodd, 1944) or be due to a special serological type of *Bact. coli* (Kirby, Hall, and Coackley, 1950). It behaves like infective gastro-enteritis in older children. The picture of primary focus, generalization, and secondary pyaemia is overshadowed by the dehydration and metabolic disturbances.

The usual secondary stage of generalization produces the most difficult clinical picture, especially if the primary focus has been slight or has been missed. I have already dealt with this to some extent in discussing problems of diagnosis. Fever, as I have already explained, may not be obvious. The gain in weight ceases, the child refuses to suck and easily tires, vomiting and diarrhoea may take place, the pulse and respirations become rapid and irregular, and there develops an ominous grey look about the child, who becomes dehydrated and inert. Oedema of the legs is often present at this stage, and this retention of fluid may mask the weight loss. Jaundice is common and may fluctuate. Blood examination shows an anaemia. Blood culture may reveal pathogenic organisms. This is the picture of what is described as sepsis neonatorum: it should never occur.

The tertiary phase is essentially pyaemic. Skin abscesses or pemphigus, or abscesses in the liver, kidney, lungs, or bones, may develop, adding to the difficulties of diagnosis. This picture may occur with almost any organism. A gonococcal ophthalmia may end with a gonococcal arthritis. Thrush in the mouth may kill by a toxaemia. The common cold, presumably of virus origin with secondary staphylococcal invasion, may lead to generalized skin sepsis. A septic circumcision wound may end with pyaemic lung abscesses. A septic vaccination may end with pyaemic abscesses in the liver. These are all examples within my own experience. There seems every justification for a conclusion reached earlier that *any* disturbance after the first few days of life should be regarded as due to infection until proved otherwise.

Prevention and Treatment

This is the essential principle of *diagnosis*, and I shall say no more about this aspect of the matter. Clearly diagnosis must precede *treatment* and if possible should include identification of the infecting micro-organisms when this is possible. This will put the use of chemotherapy and antibiotics on a rational basis. Breast-feeding must be continued whenever possible. Dehydration must be dealt with on the usual lines. The haemoglobin level must be watched. As a working rule, if this falls below 50% Haldane a blood transfusion is essential to enable the baby to overcome the infection. Local treatment must be utilized according to circumstances.

This is a very brief summary of what may be a complicated and prolonged campaign of treatment. More important is the *prevention* of infection, and in conclusion I will pick out some points for consideration in this field. On general lines the importance of the personal factor in the care of the newborn is great, as in all fields of the prevention of cross-infection. A high standard of personal hygiene must be scrupulously observed by all concerned. Adequate staff, well trained in the methods of infant care, can achieve a great deal. Figures given a year ago (Watkins, 1951) showed a reduction of a neonatal death rate from 43 per 1,000 to 24 per 1,000 in a maternity hospital in five years, during which time improved methods of care had been introduced. The use of efficient masks by the nurses and visiting staff is, I think, still important, although there is a tendency to decry their value. I do not think mothers need wear them if their babies are full-term, provided that they have no obvious upper respiratory tract infection. Visiting should be restricted to fathers, and when seeing the babies they should wear masks. Among other measures which have received attention in recent years I favour the aspiration of the gastric contents in premature babies as a routine measure in the first day or so after birth to prevent inspired material causing pneumonia. As regards care of the skin, I am still an unrepentant believer in the value of soap and water as a cleansing agent, sparingly used, followed by gentle drying with hot towels and the use of an absorbent dusting powder to mop up any remaining damp.

In a more speculative field I suggest that much might be done to raise immunity to staphylococcal infections in the newborn by the use of vaccines in the mother in the later months of pregnancy (Murray, Calman, and Lepine, 1950). This should certainly be investigated further, especially where penicillin-resistant strains of this organism are increasing. There is also a case for the energetic use of antibiotics and chemotherapy in the mother in cases of premature rupture of the membranes and prolonged labour, in the hope of preventing infection in the baby. As already suggested, there may be some association between nutritional factors and resistance to infection. More work is needed on this subject. The value of adding amino-acids to the diet of premature babies, for example, may lie more in the field of immunity than in merely provoking a better gain in weight.

There is certainly scope for research in the prevention of infection in the newborn, and it should be a profitable field, for babies saved will be unlikely to have the permanent damage which afflicts some of those treated for other neonatal maladies, such as rhesus incompatibility or cerebral trauma or respiratory failure.

My sincere thanks are due to many colleagues who have helped in the preparation of this lecture, and to them and others I am also deeply grateful for continued assistance and encouragement over many years at the various hospitals where I have been permitted to work with the newborn babies. I also owe a debt to the midwives and nursing staff, whose co-operation has been always so willing.

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AN EPIDEMIC OF INFLUENZA DUE TO VIRUS B

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A city may not be the ideal place for the conduct of precise epidemiological investigations; both its size and the complexity of its intercommunications make the course of events difficult to trace with accuracy. Nevertheless, the continued study of such epidemics is obviously essential not only because of their magnitude but also for the simple reason that most epidemics occur in cities. A large epidemic of virus B influenza in the city of Glasgow seemed a sufficiently unusual event to make it desirable to study, so far as possible, the natural behaviour of the infection in this large community. The Public Health Department of the city has, over a long period of time, paid considerable attention to the study of respiratory infection, so that it is possible to utilize statistics which might not be generally available.

Indicators of the Occurrence of an Epidemic

Accurate figures regarding the incidence of influenza are not obtainable. That infections due to influenza virus B had appeared in the city was proved by the demonstration of a rising titre of antibody in the paired sera from two cases of pneumonia which were examined on February 25, 1952. The histories obtained from these patients suggested that the earliest date of sickening was February 8, 1952. Subsequently, with the assistance of the Virus Reference Laboratory at Colindale, virus B was isolated from a fatal case of fulminating staphylococcal pneumonia. It is not intended in this report to analyse the results of the serological studies. It is sufficient to state that these, as well as other related epidemiological investigations, show beyond doubt that there was a high prevalence of virus B infection in the city during late February and March, 1952.

Some idea of the course of the epidemic can be obtained from the accumulated statistics of (*a*) the weekly new claims to the Ministry of National Insurance; (*b*) the weekly notifications of pneumonia; and (*c*) the weekly deaths from respiratory disease. These figures are supplied in Table I for the period December 1, 1951, to March 31, 1952.

(*a*) *New Claims to the Ministry of National Insurance.*—Study of these figures shows that the whole period can be divided roughly into three: the last weeks of 1951 and first week in 1952 constitute the first interval, when the figures were low; the 2nd to 8th weeks a second interval, when the figures had increased by about 50%; during the 9th to 13th weeks a further increase was noted, which reached a peak in the 10th and 11th weeks, falling in the 13th week to the pre-existing level. If the figure for the first week of the study period is regarded as 100%, then at the peak the new claims had increased to about 250%. The first interval, of course, includes the Christmas and New Year weeks, when a drop in the reporting of minor illness is a usual occurrence. When this is appreciated, the figures suggest that during the early weeks of 1952 there was a gradual increase in sickness, which culminated in the more accentuated rise in the 8th to 12th weeks.

(*b*) *Notifications of Acute Primary and Influenzal Pneumonia.*—The figures of notifications of pneumonia in Glasgow are more valuable than in many other cities. Since 1925 the practitioners have been encouraged to notify their cases, a large proportion of which are admitted to the infectious diseases hospitals. The notifications showed a rather steady increase from the first week of the study period. In the 7th week of 1952, however, a much more rapid rise began, which reached a peak in the 9th week, to return in the 13th week to a figure similar to that encountered in the earlier interval.

TABLE I.—*(a) New Claims to the Ministry of National Insurance, (b) Notifications of Acute Primary and Influenzal Pneumonia, (c) Deaths Registered from Respiratory Diseases (excluding tuberculosis); December 1, 1951, to March 31, 1952*

Week	(a)	(b)	(c)
49	3,957 (100)*	63 (100)	14 (100)
50	3,840 (97)	85 (135)	23 (164)
51	3,647 (92)	111 (176)	32 (223)
52	2,537 (39)	117 (186)	29 (207)
1	2,991 (50)	99 (157)	21 (150)
2	4,576 (116)	148 (235)	29 (207)
3	5,604 (142)	119 (189)	21 (150)
4	4,809 (122)	158 (251)	45 (321)
5	5,640 (143)	174 (277)	56 (400)
6	6,265 (159)	181 (288)	67 (478)
7	5,525 (140)	220 (350)	43 (307)
8	6,003 (152)	231 (367)	53 (378)
9	7,847 (199)	368 (585)	75 (536)
10	9,772 (247)	336 (534)	84 (600)
11	9,697 (245)	268 (426)	84 (600)
12	6,886 (147)	193 (307)	53 (378)
13	4,974 (126)	117 (186)	40 (286)
Totals ..	94,570	2,988	769

*The figures in parentheses are percentages of the figure for week 49.

The peak of notifications was reached in the week preceding the peak of new claims to the Ministry of National Insurance. At first sight this seems surprising, but it is possible that, as information of the presence of an epidemic becomes publicized, there is a greater tendency for the individual to pay attention to minor illness and to remain off work.

(*c*) *Deaths from Respiratory Diseases, Excluding Tuberculosis.*—Here, after a fairly steady number during the beginning of the period, an initial rise is noted in the 4th week, followed by a moderate increase in the 9th, 10th, and 11th weeks.

These figures combine to indicate that during the latter part of February and the first part of March, 1952,

an epidemic of some magnitude occurred in the city. It was indicated to us by general practitioners that in the majority of the cases seen by them the diagnoses were laryngitis, tracheitis, and bronchitis. The serological studies carried out in the patients admitted to the pneumonia wards showed that antibodies to virus B were present in a high proportion. The increase in the number of notifications of pneumonia and in the deaths from respiratory disease suggested either a high virulence of virus B or an enhanced susceptibility of the population. Comparison of the figures with those for the virus A epidemic of 1951, indeed, showed that the number of notifications of pneumonia was practically the same (see Table VII), although there was, fortunately, a considerable reduction in the number of deaths (see Table VI). This point will be studied in more detail later in the present report.

Pattern of the Epidemic: Contrast between the Behaviour North and South of the River Clyde

(*a*) *Pneumonia Notifications.*—It was generally rumoured that the south side of the city had experienced the effects of the epidemic earlier than the north side. The city is divided for administrative public health convenience into five divisions, of which three are on the north side of the River Clyde and two on the south side. It was therefore possible to allocate the notifications of pneumonia into the different divisions and, since the populations of the divisions were known, to compute "pneumonia rates per million." It was at once apparent that the epidemic had, in fact, appeared earlier on the south side. The figures are given in Table II; in order to complete the picture, the relevant figures for the same period of 1951–2—when virus A was epidemic—are also included.

The data support the view that the two areas of the city behaved differently. Thus, to the south of the Clyde the rise in the notification rate preceded that in the north by about three weeks. Further, whereas in the northern area the "curve" of the epidemic was sharp, with a single peak in the 10th week of the year (the usual appearance for an influenza epidemic), in the southern area the epidemic was more prolonged and there was no defined peak, although, it is true, the rate reached its maximum in the same week as in the north—namely, the 10th.

It is difficult to account for this difference in behaviour. That the River Clyde itself is more than an artificial dividing-line seems unlikely, for the amount of cross-river communication is considerable and large numbers of inhabitants, indeed, live on one side and work on the other. It may be observed from the table that in the virus A epidemic in 1951 no such difference in the behaviour of the epidemic was observed.

Since this analysis was based upon a serious manifestation of influenza—namely, pneumonia—it seemed desirable to examine data which related to less severe illness in order to see if this difference between north and south could be confirmed.

(*b*) *Absenteeism from School.*—Attendance at the 150 primary schools in Glasgow is normally fairly steady throughout the winter, the figure ranging from 87 to 92%. Records of attendances at these schools were obtained for the period December 1, 1951, to March 31, 1952. The ages of the children attending such schools lie between 5 and 12½ years. For each school the week was noted in which the peak of absenteeism occurred. The result of this analysis is shown in Table III. The contrast between the north and the south side of the city is at once apparent. In the schools on the south side of the river the peak period lay between February 22 and 29, whereas in the north the maxima lay in the period February 29 to March 7. Indeed, a spot map (Fig. 1), prepared from the data for the indi-

TABLE II.—*Notifications of Acute Primary and Influenzal Pneumonia by Civic Area and Rates per Million, December, 1950, to March, 1951, and December, 1951, to March, 1952*

Week	North of River Clyde Population: 683,300 (Northern, Central, and Eastern Divisions)				South of River Clyde Popu'ation: 385,700 (South-eastern and South-western Divisions)			
	1950–1 Notifications	Rate	1951–2 Notifications	Rate	1950–1 Notifications	Rate	1951–2 Notifications	Rate
49	73	107	43	63	56	145	17	44
50	79	115	59	86	61	158	25	65
51	103	150	82	120	66	171	22	57
52	81	118	79	115	51	132	30	78
1	168	245	66	96	68	176	28	73
2	240	350	92	134	122	316	38	98
3	223	326	73	107	85	220	37	96
4	172	251	94	137	96	249	47	122
5	119	174	104	152	52	135	65	168
6	75	110	122	178	64	166	51	132
7	63	92	120	175	41	106	92	238
8	70	102	133	194	26	67	92	238
9	91	133	155	226	35	91	102	264
10	51	74	225	329	32	83	103	267
11	66	96	174	254	36	93	90	233
12	60	88	126	184	34	88	56	145
13	74	108	82	120	42	109	30	78
Totals	1,808		1,829		967		925	

TABLE III.—*Peak Period of Absenteeism in 150* Primary Schools in the City of Glasgow*

Area	Number of Schools with Peak Absenteeism in Week Ending					Total
	15/2/52	22/2/52	29/2/52	7/3/52	14/3/52	
North	1	8	44	42	1	96
South	9	20	24	0	0	53
Totals ..	10	28	68	42	1	149*

* One school showed no peak.

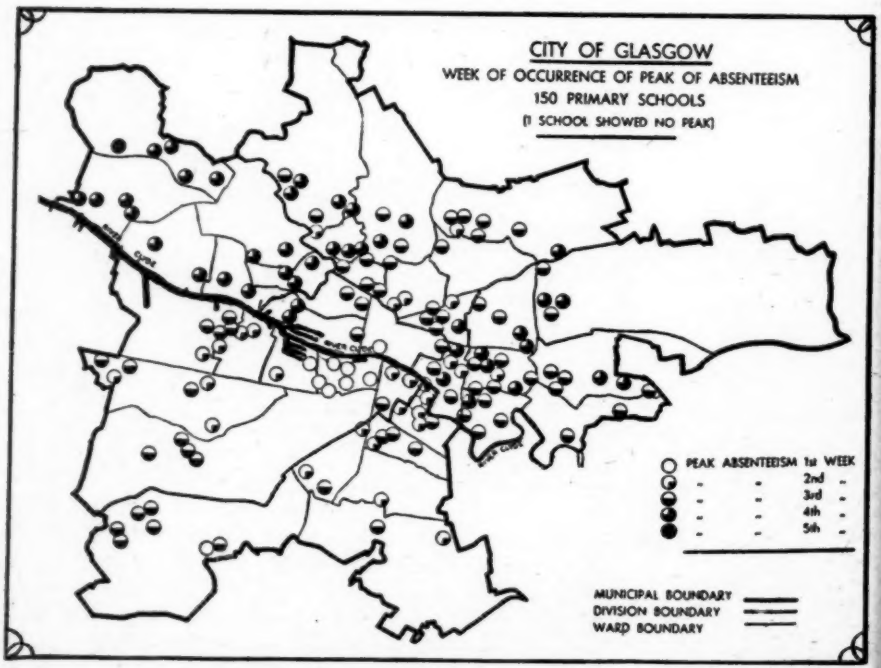

FIG. 1

vidual schools, shows that practically all of the schools in which the peak absentee rate occurred in the first week (week ending February 15, 1952) were in one area lying along the south bank of the River Clyde. This district includes a number of industries as well as an overcrowded, badly housed population, and contains one of the main receiving docks. It is into this dock that the bulk of the coastal and Continental trade is received. The spot map also gives the impression that the epidemic spread from this focal centre, and it will be seen that those schools situated in the extreme north-west of the city were the last to be affected and that all showed their peak of absenteeism at the end of the period. The distribution of the data by administrative Public Health Divisions brings out this point very well. The gradual ascent of the mean week throughout the five divisions suggests that there was a gradual spread of infection through the city from a focal area (Table IV).

TABLE IV.—*Distribution of School Absenteeism by Public Health Division and Week*

Week ending:	15/2/52	22/2/52	29/2/52	7/3/52	14/3/52	Mean Week
South-western ..	7	10	12	0	0	2·17
South-eastern ..	2	10	12	0	0	2·42
Central	0	5	19	11	0	3·17
North-eastern ..	0	3	21	12	0	3·27
North-western ..	1	0	4	19	1	3·76
Totals ..	10	28	68	42	1	

Meteorological Conditions

Scotland in general and Glasgow in particular experienced an unusually severe spell of cold weather in the early part of 1952. It was therefore decided to study the available meteorological information. Some of the data are shown in Fig. 2. For comparison, the information for the same periods of 1950 and 1951 has been extracted and is shown as mean figures. There are three interesting features. First, it will be seen that the relative humidity, after a rather high reading for two weeks, fell to a very low figure during the week in which the epidemic is assumed from the serological studies to have begun; secondly, that the minimum temperature was unusually low in the immediately preceding period; and, thirdly, that the average daily range of temperature was much greater than usual during the early part of the year.

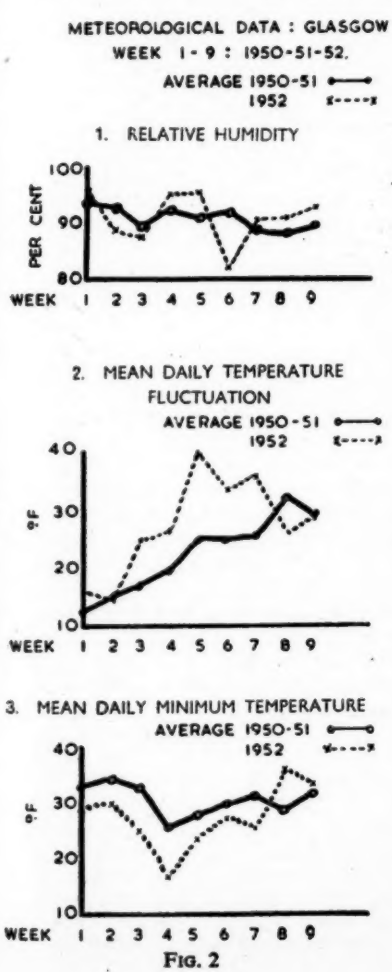

FIG. 2

These conditions, of course, applied to the city as a whole and leave unexplained the curious difference in behaviour between the north and south of the city.

Situation in the Rest of Scotland

There is no doubt that the facility with which the admission of cases of pneumonia to hospital in Glasgow is secured encourages the practitioner to notify his patients. He will naturally tend to notify more readily patients in those age-groups in which the disease may still run a severe course, as well as those living in unsatisfactory housing conditions. Nevertheless, where notification is assiduously practised the figures serve, as has been seen, as a useful indicator of the prevalence of respiratory infection. A perusal of the statistics for four other Scottish cities yields less valuable information. The figures for Edinburgh, Aberdeen, Dundee, and Greenock relating to "pneumonia notifications" and "deaths from respiratory diseases (excluding tuberculosis)" show that on quite a number of occasions the deaths exceed the notifications. In these circumstances less importance can be attached to the notifications, although it may be stated that an examination of them does not suggest that there was any very unusual occurrence during the last four weeks of 1951 and the first ten weeks of 1952. The new claims made to the Ministry of National Insurance have been abstracted and are shown in Table V. It will be observed that in Edinburgh the figures fluctuated between 53% and 123% of the mean for the period; in Dundee a peak of 125% of the mean was encountered in the third week of the year; in Aberdeen the thirteenth week showed a figure 160% of the mean for the period. In Greenock—which lies twenty-six miles to the west of Glasgow on the south side of the River Clyde—the last three weeks of the period produced figures ranging from 125 to 139% of the mean. The intercommunications between Glasgow and Greenock are considerable, so that it would not be surprising if the epidemic in the city had extended out to the surrounding district. Additional evidence, not presented here, from the Ministry of National Insurance new claims in other parts of the West of Scotland supports such a view.

TABLE V.—*New Claims to the Ministry of National Insurance, 1951–2. Figures for Five Scottish Towns*

Week	Edinburgh	Dundee	Aberdeen	Greenock	Glasgow
48	1,326 (85)*	616 (94)	563 (82)	280 (86)	3,971 (73)
49	1,369 (88)	683 (104)	616 (89)	240 (74)	3,957 (72)
50	1,244 (79)	616 (94)	575 (83)	266 (82)	3,840 (70)
51	1,326 (85)	602 (92)	649 (94)	220 (68)	3,647 (67)
52	831 (53)	444 (68)	433 (63)	167 (51)	2,537 (46)
1	992 (63)	477 (73)	509 (74)	213 (65)	2,991 (55)
2	1,616 (104)	757 (85)	657 (95)	299 (92)	4,576 (84)
3	1,831 (117)	816 (125)	822 (119)	378 (116)	5,604 (102)
4	1,633 (104)	763 (117)	720 (104)	348 (107)	4,809 (88)
5	1,779 (114)	721 (110)	721 (105)	371 (114)	5,640 (103)
6	1,931 (123)	797 (122)	797 (116)	428 (131)	6,265 (115)
7	1,638 (105)	686 (105)	707 (103)	400 (123)	5,525 (101)
8	1,488 (95)	629 (96)	694 (101)	329 (101)	6,003 (110)
9	1,463 (93)	562 (86)	651 (94)	319 (98)	7,847 (144)
10	1,348 (86)	503 (77)	629 (91)	317 (97)	9,772 (179)
11	1,364 (87)	595 (91)	714 (104)	408 (125)	9,697 (178)
12	1,298 (83)	679 (104)	840 (122)	424 (130)	6,886 (126)
13	1,332 (85)	706 (108)	1,102 (160)	453 (139)	4,974 (91)
Totals	25,809	11,652	12,399	5,860	98,541
Mean week for period	1,434 (100)	654 (100)	689 (100)	326 (100)	5,476 (100)

* The figures in parentheses are percentages of the mean for the period.

Mortality from the Epidemic

The deaths which occurred from respiratory diseases during the two periods of four months, December–March, 1950–1, and December–March, 1951–2, are shown in Table VI. It has already been explained that in 1950–1, in common with the rest of Great Britain, Glasgow experienced an epidemic of virus A influenza during December–January (Grist *et al.*, 1952). It is therefore of interest to compare that epidemic with the one due to virus B, which ran through

TABLE VI.—*Comparison of Mortality in Two Periods: December–March, 1950–1, and December–March, 1951–2*

Month	1950–1		1951–2	
	Confirmed Pneumonia Notifications*	Total Deaths from Respiratory Diseases	Confirmed Pneumonia Notifications*	Total Deaths from Respiratory Diseases
December ..	567	155	276	55
January ..	1,233	265	500	74
February ..	413	131	818	136
March ..	367	101	926	131
Totals ..	2,580	652	2,520	396

* In this table and Table VII the figures abstracted are those for confirmed notifications, since the age-grouping is more easily available for such cases.

February–March, 1952. The much greater mortality arising during the influenza A epidemic is at once apparent.

This difference between the two epidemics was studied more closely. It seemed, in particular, desirable to demonstrate whether the lower mortality in the present epidemic could be explained by a difference in the age distribution of the persons attacked. Accordingly, the confirmed notifications were obtained for these two four-months periods in 1950–1 and 1951–2 (Table VII). In the two non-epidemic periods (February–March, 1951, and December, 1951–January, 1952) the age distributions were almost identical. In the epidemic period December, 1950–January, 1951, it seems that some excess of cases was encountered in the very young and elderly compared with the epidemic period February–March, 1952. The similarity, however, of all four curves is a striking feature and, if nothing else, might indicate that the general practitioners adopt a fairly uniform standard in notification. The similarity of the two non-epidemic periods has encouraged us to use the figures to estimate the age distribution of the excess of pneumonias which might be regarded as the product of the influenza virus epidemics. It will be seen that the distributions show slight differences, particularly in the excess of young children in the 1950–1 epidemic. Such differences as there are, however, lend no support to the view that the difference in mortality in the two periods could be explained in terms of the age distribution of the notified cases.

TABLE VII.—*Age Distribution of Confirmed Notifications of Pneumonia: December to March, 1950–1, and December to March, 1951–2*

Period	Age Group (Years)							
	0–5	–10	–15	–25	–45	–60	60+	Total
December–March, 1950–1	877	133	65	152	327	413	613	2,580
December–March, 1951–2	719	183	90	185	371	424	548	2,520
December–January, 1950–1 (epidemic period A)	656	82	46	114	218	270	414	1,800
February–March, 1952 (epidemic period B)	491	132	77	122	263	289	370	1,744
February–March, 1951 (non-epidemic period)	221	51	19	38	109	143	199	780
December–January, 1951–2 (non-epidemic period)	228	51	13	63	108	135	178	776
Increment of pneumonia notifications due to epidemic A ..	428	31	33	51	110	135	236	1,024
	*(188)	(61)	(254)	(81)	(102)	(100)	(133)	
Increment of pneumonia notifications due to epidemic B ..	270	81	58	84	154	146	171	964
	*(122)	(159)	(305)	(221)	(141)	(102)	(86)	

* The figures in parentheses represent the percentage increase over the relevant non-epidemic period.

Discussion

It is generally thought that, whereas influenza A infections usually occur in rather short sharp epidemics which may be geographically widespread, outbreaks due to type B virus tend to be smaller, more sporadic, and diffuse both in place and in time. The recent Glasgow experience is therefore interesting in that a large and distinct epidemic, confined within a period of roughly five weeks and not associated with noteworthy outbreaks in geographically related areas, was attributable to the relatively innocuous type B virus.

The similarity between the total numbers of cases of pneumonia encountered in two epidemics—the first due to virus A, the second to virus B—is surprising. The greater virulence of virus A would lead one to expect an increase of cases of pneumonia as well as an increase in the deaths from respiratory diseases. It seems not unlikely that the role of influenza virus in the production of pneumonia may be the carrying out of a "softening-up" process preparatory to bacterial invasion; the more extensive the damage to the respiratory mucosa the greater the risk of successful bacterial assault and, consequently, of secondary pneumonia. These two succeeding episodes in Glasgow, almost equal in magnitude as measured by the resultant pneumonias, suggest that in circumstances favourable to it the type B virus may show characteristics not unlike those of type A. The importance of the virulence of the primary virus infection becomes more obvious when attention is directed to the total mortality produced. The mortality rates—based on confirmed notifications and deaths from respiratory diseases—in succeeding epidemics due to virus A and virus B, were 25% and 16% respectively; and, although these rates must not be regarded as expressing a true mortality from pneumonia, they are nevertheless indices which can be compared. It will be interesting to examine in exact detail the pattern of the bacterial flora of the sputum from the pneumonia patients in the two periods, but a preliminary survey has not indicated any gross dissimilarity. Even allowing for the suggestion that the age distribution of the cases of pneumonia in the more recent (B) epidemic may have been more favourable, it cannot be doubted that the A virus has a greater capacity to induce fatal disease. Although there is nothing new in this statement, the fact that the conclusion is drawn from the experience of the same population with the two viruses in a comparatively short period of time may give it added value.

That the climatic conditions played a part in creating a suitable soil for the production of an epidemic seems worthy of consideration. Fluctuations in relative humidity accompanied by a wide daily temperature range must make considerable demands upon the activity of the mucosa of the respiratory tract. With a virus which has *per se* a high virulence factor, climatic changes would seem to have little importance. On the other hand, with a virus whose virulence is normally low, climatic changes might induce variations in host resistance which would alter the balance in favour of the invader.

Such an argument could have been advanced more persuasively if the whole of Glasgow had behaved in a similar fashion. The difference between the north and south of the city introduces a further surprising feature and, moreover, one which tends to lessen the importance of the climatic changes. As we have already said, we find it hard to believe that the River Clyde constituted a factual dividing-line between two areas. There seems to be no doubt, however, that the south side of the city experienced an earlier and more prolonged epidemic than the north. Without wishing to appear to over-simplify the problem, it is an interesting fact that the epidemic began in that area of the city which adjoins the dock into which much of the Continental traffic is received. Influenza due to virus B was recorded in the bulletins of the World Health Organization in Denmark in mid-November, 1951, in the Netherlands in the last week

of December, 1951, and in Italy in January–February, 1952. The vessels which arrived at this dock from the middle of January until the end of February were as follows:

Date of Arrival in Glasgow	Nationality	Last Port of Call
15/1/52	British	Antwerp-Ghent
18/1/52	Swedish	Rotterdam
23/1/52	British	Antwerp-Ghent
30/1/52	,,	,,
4/2/52	Dutch	Honfleur
6/2/52	British	Antwerp-Ghent
7/2/52	,,	Paris
8/2/52	,,	Lisbon
13/2/52	,,	Antwerp-Ghent
19/2/52	,,	,,
22/2/52	Dutch	Rouen"
26/2/52	British	Antwerp-Ghent
29/2/52	Swedish	Valencia-Malaga

It is a possible speculation that virus B was introduced to the city from one of these ships; that the weather conditions prevailing increased the chances of spread into the adjoining area of the city; that a local "build-up" occurred among an overcrowded population, which enhanced the virulence of the virus and encouraged a later spread to the rest of the city and to the surrounding district. We are of course aware of the occurrence of small groups of cases in parts of England during the same period of time, so that it may be unwise to over-emphasize the possibility of the introduction of the virus from overseas.

The analysis of the age distributions of the notified cases of pneumonia seems interesting. Little or no accurate information is available of the actual age-distribution of influenza in a community. One might have expected, however, that the increment of pneumonias resulting from influenza virus infection would have upset the age distribution of the normal run of endemic cases. In fact, the point which emerges is that in two epidemic periods due to different viruses and in two non-epidemic periods the age distributions of the notified cases followed an essentially similar pattern. When the age groups are studied in detail individual differences emerge. It is not perhaps surprising that there should be considerable increases in the age groups under 5 and over 60 years. The interrelationship of influenza and pneumonia at the extremes of life is obscured by the epidemic inexperience of the young and the presence in the elderly of chronic respiratory disease or degeneration—factors which must enhance the possibility of successful bacterial assault. It is interesting to find that the greatest absolute increase in pneumonia notifications in the 1950–1 A epidemic occurred in the 0–5-year age group. When the 1952 B epidemic is compared with the 1950–1 A epidemic the most striking feature is the increase of notifications in the middle age groups (6–45 years). These figures would support a view that the A virus was attacking a population with a relatively high immunity from recent experience, whereas the B virus was operating in a community whose immunity was of a low order. The presence of B virus in Glasgow during the spring of 1950 is known from the observation of an antibody rise in a small proportion of the pneumonia admissions; but there was no large-scale epidemic at this time. It may be assumed that Glasgow shared in the European experience of A infection in the winter of 1948–9, although there is no supportive laboratory evidence. Our findings may simply reflect the much more widespread impact which the A virus makes on the community, but the possibility of a difference in the degree or persistence of immunity cannot be excluded.

Summary

An epidemic of influenza B in the city of Glasgow during the early months of 1952 is reported.

The figures for new claims to the Ministry of National Insurance, pneumonia notifications, and deaths from pneumonia during the period of the epidemic are compared with those obtained in the epidemic of influenza A which occurred in the city during the winter of 1950–1. From these figures it was found that similar numbers of persons were affected in the two periods, and that the increase in pneumonia notifications was of the same order. The age distribution of the deaths from pneumonia differed in the two epidemics: in the influenza A epidemic the greater number of cases was in the youngest and oldest groups. The A epidemic was associated with the higher mortality.

The possible origin of the recent epidemic in the dock area, and its spread throughout the city, are discussed in association with the figures for school absenteeism in February and March.

The abnormal meteorological conditions which preceded the epidemic are noted.

We wish to thank Dr. Ian Sutherland, of the Department of Health for Scotland, for assistance in obtaining data from other Scottish cities, and also various members of the staff of the Public Health Department of Glasgow for their co-operation. We are indebted to Mr. G. H. Garside, Director of Parks, for supplying meteorological data.

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STAPHYLOCOCCAL PYOTHORAX IN INFANTS

BY

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Empyema in infants was not uncommon before the days of penicillin. Chaplin (1947) reported 104 cases under 2 years of age admitted to an English hospital in a 10-year period. From America Spence (1920), Brown (1923), Steinke (1935), Hochberg and Kramer (1939), and Forbes (1946) all report large series. Spence (1920) noted the incidence as about one to every nine cases of pneumonia admitted to hospital in his and other series. The role of the staphylococcus in empyema in infants appeared to increase with the advent of sulphonamides (Forbes, 1946; Chaplin, 1947). Frazier and Davis (1951) found that all of 14 cases of empyema in children under 12 months old which occurred since 1943 were due to the staphylococcus.

In the past five years empyema has been much less common. Frazier and Davis (1951) found that empyema did not develop in any of their patients with pneumonia who had had adequate penicillin. In spite of this, staphylococcal empyema is still seen in infants' wards, though it receives little or no special mention in most standard textbooks on paediatrics. Early recognition is most important, and the best treatment is not yet established. Two successfully treated cases in infants in the first month of life are here reported.

Case 1

A previously normal 16-day-old male infant was admitted on February 27, 1951, having had difficulty in breathing for 24 hours. He did not seem very ill, but his temperature was 100.2° F. (37.9° C.), his respirations 44, and a definite patch of crepitations was audible over the right chest. Intramuscular penicillin, 50,000 units six-hourly, was begun, and although his temperature settled, his general condition altered little until the fourth day, when he suddenly became cyanosed and very distressed. The right chest was dull to percussion, breath sounds were absent, and an *x*-ray film showed complete opacity of the right lung field with slight mediastinal shift to the left—a shift which could not be

detected clinically. His colour improved after he was placed in an oxygen box, but next day he was much worse. Feeding at the breast was impossible, and his weight dropped to 5 lb. 12 oz. (2.6 kg.). On March 6 he was almost moribund. As the dullness had increased, the right chest was needled; this produced 90 ml. of moderately thick blood-stained pus which grew penicillin-sensitive *Staphylococcus aureus* on culture. Penicillin, 200,000 units, was introduced into the pleural cavity and some air also accidently leaked in. *X*-ray films showed a hydropneumothorax with no evidence of loculation. After aspiration the infant's condition improved, but he remained very ill, and became cyanosed if left out of oxygen for more than a minute or if nursed otherwise than on his right side.

During the six days following the first needling a total of 85 ml. of pus was removed at five aspirations and 1,000,000 units of penicillin was instilled on each occasion. The last two specimens were sterile, and thereafter no more fluid could be obtained; *x*-ray films showed collapse of the right lung but no fluid. In the next month marked re-expansion was seen radiologically, and clinical improvement was hastened by two blood transfusions. The infant was discharged from hospital on June 8, his chest being clinically and radiologically normal. When seen as an outpatient in March, 1952, there was no evidence of pleural thickening.

Case 2

A female infant, 25 days old, was admitted on May 20, 1951. Delivery—in hospital—had been normal and progress uneventful until constipation and irregular breathing were noted on the day before admission. She became cyanosed and was admitted four hours later, a wasted though not dehydrated infant with a temperature of 100.2° F. (37.9° C.) and slight dullness and harsh breathing in the right chest. She was treated for pneumonia of the right lung in an oxygen box and given intramuscular injections of 50,000 units of penicillin three-hourly and 200 mg. of streptomycin twice daily, this combination having been found efficacious in the severer pneumonic conditions in infants during the preceding winter. The blood count next day was: Hb, 74%; white cells 4,800 per c.mm. (neutrophils 46%). Material was not obtained for bacteriology, and *x*-ray films were not taken in the first few days.

The infant's condition remained poor, and she was very weak and cyanosed when removed from the oxygen box for feeds. On the fourth day the percussion note became dull and, although no mediastinal shift was detectable clinically, empyema was suspected. An *x*-ray film in the erect position showed a completely radio-opaque right thorax with no fluid level, and shift of the mediastinum to the left. On May 24, 2 ml. of thin greenish pus was aspirated from the right thorax and 75,000 units of penicillin instilled. A pure growth of coagulase-positive *Staph. aureus*, insensitive to 1,000 units penicillin per ml. but sensitive to streptomycin, was cultured from the pus. Next day 30 ml. of pus was aspirated and 1,000,000 units of penicillin instilled. Intramuscular penicillin and streptomycin were continued, and daily or twice-daily aspiration was performed, the amount withdrawn varying from 3 to 80 ml. of pus. Penicillin, 1,000,000 units, and latterly streptomycin, 100 mg., were instilled on each occasion.

The infant's condition was becoming very poor, although after the first aspiration the temperature dropped to normal and remained there. She was nursed on the affected side in the oxygen box, and fed in the box. Feeds were taken with very great difficulty and an attempt to give aureomycin (100 mg. twice daily) by mouth had to be abandoned. If laid on the left she rapidly became distressed and blue. The worst phase coincided with pus under obvious pressure in the thorax, and aspiration usually produced some relief, but was hampered by blocking of the needle by small clots. By May 30 there was some improvement. *X*-ray films showed almost complete collapse of the right lung by air in the pleural cavity, and a minimum of fluid. However, two days later fluid had reaccumulated and 65 ml. of pus was aspirated. From every specimen a staphylococcus was grown which remained insensitive to penicillin but sensitive to streptomycin, aureomycin, chloramphenicol, and terramycin. Intrapleural instillation of aureomycin was tried, 50 mg. of the intravenous preparation being given well diluted. This produced a spike of temperature, though further instillation of 25 mg. produced no ill-effect. However, the pus still contained staphylococci. It was now possible to give concurrent aureomycin by mouth, but this produced diarrhoea after six days. All parenteral therapy was abandoned.

The infant was now taking feeds better and, although still in an oxygen box, breathing was much improved. During aspirations, administration of 100% oxygen by anaesthetic mask greatly diminished the disturbance of these procedures. But she was becoming very wasted, and at the age of 7 weeks weighed only 6 lb. 4 oz. (2.8 kg.). Her haemoglobin had dropped to 40%. On June 11 intrapleural terramycin was begun and 100 mg. was instilled daily for 10 days. In view of the plugs which hindered complete aspiration, 5,000 Christensen units of streptokinase were also instilled daily, and this seemed to render aspiration easier. The pus still contained staphylococci, but the colonies were now very scanty, and took 48 hours to develop. Resistance to antibiotics was unchanged. Assay of pus withdrawn 24 hours after instillation showed it to contain a bacteriostatic concentration of terramycin. After cessation of terramycin therapy large amounts of sterile pus continued to accumulate; but a week later, on June 27, pus was aspirated for the last time.

The infant's condition now improved rapidly. The right lung at first showed complete collapse but aerated after two weeks. On discharge from hospital in September she weighed 12 lb. (5.4 kg.) and her haemoglobin was 70%. There was some upper-lobe collapse, but the lower lobe was well aerated. There were no respiratory symptoms, and no clinical or radiological evidence of residual fluid. In March, 1952, her weight was normal and she was very well, but there was mediastinal shift to the right, and *x*-ray films still showed a collapsed upper lobe.

Aetiology

Staphylococcal empyema in infants probably always follows staphylococcal pneumonia. In some cases *x*-ray films have shown in the underlying lung cyst-like cavities which later disappear and are typical of staphylococcal infection (Philips and Kramer, 1945). In about 40% of cases the empyema is associated with spontaneous pneumothorax (Forbes, 1946; Ellis, 1951). Leigh Collis and Foster-Carter (1940) reported a spontaneous pneumothorax in an infant in which at necropsy the underlying lung showed multiple minute staphylococcal abscesses, one of which had burst into the pleura. A similar accident probably accounts for most staphylococcal empyemas in infants, and post-mortem descriptions by Glaser and Epstein (1931) and Macgregor (1936) reveal comparable findings. In the two cases reported here no pneumothorax was present before aspiration, but it is probable that some of the considerable amount of air later demonstrated in the thorax was due to a bronchopleural fistula occurring during treatment, and that this is a factor in preventing loculation and maintaining a total pyopneumothorax. This tendency to total pyothorax—often with air under tension—is evident in many of the reported cases occurring in the first few months of life.

Frazier and Davis (1951) mention a seasonal incidence, the first half of the year being incriminated. The cases reported here occurred during this period, and during or following an influenza "A" epidemic. Gibson and Belcher (1951) have re-emphasized the relationship between staphylococcal pneumonia and epidemic influenza.

Diagnosis and Treatment

The essential step in establishing the diagnosis is needling the chest, and this should not be delayed. Any respiratory

infection with delayed resolution in an infant should raise the possibility of empyema; the presence of dullness to percussion makes the diagnosis likely (Glaser and Epstein, 1931). Other signs may be deceptive. Breath sounds may not be greatly altered, mediastinal shift may not be detectable, and the infant is often too ill to enable a technically adequate *x*-ray picture to be taken, though this may be of great help in the differentiation from collapse. Clubbing did not appear in the two cases reported here, and other authors do not stress it. In Case 2 a white blood count showed a granulocytopenia early in the disease.

Most authors agree that repeated aspiration with penicillin instillation should be tried before other treatment is contemplated (Ellis, 1951). Chaplin (1947) found that in children of all ages aspiration alone failed to cure 13 out of 21 staphylococcal empyemas, but of 4 infants under 6 months intercostal drainage was necessary only in one. In Case 1 the pus was sterile after six aspirations, and thereafter no further fluid could be obtained. Rapid sterilization of the pus with a small number of aspirations is often reported. A few cases even responded rapidly to aspiration before penicillin or sulphonamides were available (Spence, 1920). It is obvious that surgical drainage is unnecessary in these cases and is unlikely to hasten their recovery.

In pyothorax, whether air is present or not, the thoracic contents may be under pressure, and aspiration relieves the clinical condition dramatically. This was found not only at the initial needling but on later occasions, when aspiration was delayed for more than 24 hours in the belief that the fluid had resolved. Aspiration should be carried out daily, as, even though the pus may seem to be decreasing, rapid reaccumulation may be disastrous. Sterilization of the pus seems to prevent its reaccumulation; the chronic sterile collection of pus known in adults as "penicillin empyema" has not been reported in infants.

In Case 2 the staphylococcus was resistant to penicillin from the outset and, although it remained sensitive to streptomycin *in vitro*, local streptomycin failed to sterilize it. Intrapleural aureomycin was tried, but instillation of 50 mg. at a time proved too irritant. Smaller amounts did not affect the staphylococcus, probably because aureomycin is not stable in solution. No preparation of chloramphenicol for local use was available and therefore an intravenous preparation of terramycin was tried: 100 mg. intrapleurally produced no reaction, and 24 hours later only a very attenuated growth of the staphylococcus was obtained. In addition, a bacteriostatic concentration of terramycin was found in the pus after 24 hours, and there is little doubt that the sterilization of the pus and the infant's recovery were due to this antibiotic.

Few published accounts of staphylococcal pyothorax in infants mention residual effects on lung function. In Case 1 the child was apparently normal a year later. In Case 2 there was residual upper-lobe atelectasis after nine months.

The place of surgical drainage by intercostal tube is still not decided. The good immediate results obtained by this treatment suggest that it is indicated when daily aspiration and instillation of antibiotics fail to sterilize the pus within two weeks. It was probably indicated in Case 2, but it is doubtful if full expansion of the lung would thereby have been achieved.

Summary

Two cases of stapyhylococcal pyothorax following pneumonia in infants in the first month of life are described. Both responded to aspiration and sterilization of the pus by intrapleural antibiotics. Aetiology, diagnosis, and treatment are discussed.

I am indebted to Drs. D. W. G. Smith and B. D. R. Wilson for permission to publish and for their help and encouragement, and to Dr. F. C. Valentine for the terramycin and for his advice. I would like to express my appreciation of the efforts of Miss M. Brailsford and her staff, without whose devoted nursing care neither infant could possibly have survived.

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IMMUNITY OF THE NEWBORN

A STUDY OF THE TRANSFER OF ANTI-STREPTOLYSIN FROM MOTHER TO FOETUS DURING PREGNANCY

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Interest in the transfer of antibodies across the placenta has increased since the observation that cord blood may contain more antibody than that of the mother. Most of the work within recent years has been concerned with diphtherial and staphylococcal antibodies.

In order to extend the range of bacterial antibodies investigated in this way it was decided to estimate in mothers and their newborn children the blood level of antibodies to another common infecting organism. For this purpose the streptococcus was chosen because of its ubiquity, and also because there are available convenient methods of estimating anti-streptolysin. The results obtained in this investigation have amply confirmed the high antibody level previously observed in the cord blood of newborn infants.

Materials and Methods

Blood Samples.—Cord blood was obtained at delivery, and each mother was bled by venepuncture, either immediately before or soon after delivery. Samples were collected in dry tubes and allowed to clot.

Streptolysin.—The bacterium used for the preparation of the streptolysin was a culture of Group A III *Streptococccus pyogenes* (strain No. S 84) obtained from the State Serum Institute, Copenhagen. According to Todd (1932) two streptolysins can be obtained from haemolytic streptococci of Lancefield's Group A, C, or G. One, streptolysin O, is oxygen-sensitive, and the other, streptolysin S, is oxygen-stable but heat-sensitive, and can be extracted with serum. Throughout the whole series of experiments here described a single preparation of streptolysin O was used, and this was prepared according to the method of Kalbak (1942), described in his modification of the anti-streptolysin titration technique of Todd (1932). The minimum haemolytic dose (M.H.D.) of the streptolysin was checked repeatedly, and remained constant from the beginning to the end of the series. Storage was at 4° C. under a layer of sterile liquid paraffin 1 in. (2.5 cm.) thick.

Standardization of Streptolysin.—Doubling dilutions of streptolysin were made in buffer from 1/2 to 1/256 so that

each tube contained 1 ml. To every tube were added 1 ml. of buffer and 0.5 ml. of washed rabbit cells. The last tube showing complete lysis throughout this series was 1/8. For the tests a 1/5 dilution was used, this being slightly less than 2 M.H.D.

Buffer Solution.—The buffer solution used for dilution and suspension of rabbit cells was composed of 4.8 g. NaCl, 1.45 g. KH_2PO_4 (anhydrous), and 7.6 g. $Na_2HPO_4.2H_2O$ dissolved in one litre of distilled water.

Cell Suspension.—For each batch of tests a fresh 5% suspension in buffer of washed rabbit cells was prepared. The same rabbit was used for the whole series, in order to avoid variation in rabbit-cell fragility. The blood used was never less than 24 hours and never more than four days old; as a rule the rabbit was bled the day before a batch of tests.

Technique

Maternal and cord blood sera were diluted 1/10 with buffer after inactivation by heating in the water-bath at 56° C. for 30 minutes. Doubling dilutions were made of the diluted sera in buffer from 1/40 to 1/1,280, so that the total volume in each tube was 1 ml. Separate pipettes were reserved for each of the reagents, and special pipettes for making serial dilutions. To each tube was added 1 ml. of diluted streptolysin (0.2 ml. streptolysin + 0.8 ml. buffer), thus providing just less than 2 M.H.D. The tubes now containing 2 ml. were shaken individually to ensure complete mixing, and 0.5 ml. of the 5% rabbit cell suspension was added. The tubes were again shaken individually and then heated for 45 minutes, about half immersed in the water-bath at 37° C.

After inspection the tubes on either side of the apparent end-point were centrifuged and re-examined. The end-point was taken as the first tube which showed any naked-eye haemolysis. The degree of haemolysis was estimated with an M.R.C. grey wedge photometer, the supernatant being diluted with buffer where necessary to obtain a reading on the scale. This method proved remarkably accurate. For example, complete haemolysis of the standard volume of cells consistently gave a reading of 96 when the supernatant was diluted 1 in 4.

Inhibitory Serum Factors

Certain factors in serum may interfere with tests which use haemolysis as an indicator. The inhibitory effect of cholesterol is well known, but it is accepted that as a rule cholesterol in the cord blood is substantially below the maternal level. In consequence cholesterol was disregarded as a possible cause of the high infant levels recorded. For the same reason phospholipids were discounted.

Another substance considered was ascorbic acid, not only because it has been reported to be much higher in cord blood than in that of the mother (Mindlin, 1940), but also because of its effect on haemolysis (Traina, 1949).

Since Traina used very large amounts of ascorbic acid, it seemed extremely unlikely that inhibition due to this substance could affect our experiments. Nevertheless, experiments were made with sera to which ascorbic acid had been added. Umbilical-cord blood levels of 1.2 to 2.48 mg./100 ml. have been reported by Mindlin (1940) for plasma and by Barnes (1947) for whole blood. Consequently sera containing approximately ten times these concentrations were tested in parallel with control sera to which no ascorbic acid had been added. The results in every pair of tests were identical, and indicated that levels of ascorbic acid to be found in cord blood would not influence the experiments.

Results

Anti-streptolysin O was titrated in the sera of 46 mothers and their babies. The results of the consecutive series are presented in Table I, where the visual end-points are recorded according to titre. It was found that in 33 out of the 46 cases the cord blood level was at least twice that of the mother's blood. In one instance (Case 38) both levels were too low to demonstrate a difference under the conditions of the test; while in the remaining 12 cases the first tube to show haemolysis was the same for both mother and child, although in most of these there was a noticeable naked-eye difference in degree of haemolysis between the two. When this difference was estimated with the grey wedge photometer it was found that in eight cases the anti-streptolysin was higher in cord blood than in the maternal blood, in three cases the levels were approximately equal, while in only one instance was the maternal level the greater. The results of the photometer readings are shown in Table II.

TABLE I.—*Comparative Titrations of Anti-streptolysin O in Maternal and Cord Blood Sera*

Case No.	Anti-streptolysin O Titre (Reciprocal)		Higher Level	Case No.	Anti-streptolysin O Titre (Reciprocal)		Higher Level
	M.	C.			M.	C.	
1	640	1,280	C	24	80	320	C
2	640	1,280	C	25	40	160	C
3	160	160	*	26	160	320	C
4	160	320	C	27	160	320	C
5	160	640	C	28	40	40	*
6	160	320	C	29	80	160	C
7	320	640	C	30	640	640	*
8	160	320	C	31	40	80	C
9	160	160	*	32	160	320	C
10	80	160	C	33	40	40	*
11	80	160	C	34	160	320	C
12	160	320	C	35	160	160	*
13	160	160	*	36	80	80	*
14	320	320	*	37	80	80	*
15	160	320	C	38†	<40	<40	
16	320	640	C	39	80	160	C
17	80	160	C	40	320	640	C
18	80	160	C	41	160	640	C
19	80	160	C	42	160	320	C
20	160	160	*	43	40	80	C
21	320	320	*	44	160	320	C
22	40	80	C	45	80	160	C
23	40	80	C	46	320	1,280	C

C.=Cord. M.=Maternal.

* In 12 cases the end-point tubes gave the same titre although haemolysis was not always equal. Estimated differences in degree of haemolysis are shown in Table II.

† Both maternal and cord levels were too low to be recorded under the conditions of the test.

TABLE II.—*Estimation of Degree of Haemolysis in the Supernatant at the End-point*

Case No.	Maternal		Cord		Higher Level of Anti-streptolysin
	Dilution	Photometer Reading	Dilution	Photometer Reading	
3	4 ×	84	Undil.	65	Cord
9	4 ×	78	,,	63	,,
13	Undil.	54	,,	132	Maternal
14	,,	115	,,	85	No significant difference
20	4 ×	54	4 ×	84	,,
21	4 ×	75	Undil.	52	Cord
28	4 ×	87	,,	92	,,
30	4 ×	78	,,	98	,,
33	4 ×	96	2 ×	43	,,
35	4 ×	72	2 ×	31	,,
36	Undil.	33	Undil.	35	Equal
37	4 ×	75	2 ×	43	Cord

The degree of haemolysis was used to interpolate empirical values of anti-streptolysin between the 100% differences achieved in the test proper recorded in Table I. The greater the titre of anti-streptolysin present the lower was the degree of haemolysis. Complete haemolysis of the standard dose of cells was found to give the reading 96 when tubes were diluted 1 in 4.

In the series of 46 cases it was found that the cord blood contained more anti-streptolysin than the maternal blood in 41, the levels were approximately equal in three, the maternal level was higher in one, and in one case the levels were too low for the test.

Discussion

This investigation shows that in the great majority of cases anti-streptolysin levels are much higher in cord blood than in maternal blood. This finding was not unexpected, in view of the high antibody levels in the cord blood reported with diphtheria toxin (Barr *et al.*, 1949) and with staphylococcal toxin (Murray *et al.*, 1950). It does, however, provide

another example of high antibody content of foetal blood, and in this respect confirms the previous findings. A striking feature of the results is the consistent relationship between the mother's and the infant's antibody level as well as the magnitude of the latter.

The significance of these findings, and the revised view of placental permeability to antibodies to which they lead, was discussed in a previous paper (Calman and Murray, 1951). In that paper we concluded that the simple filtration hypothesis was becoming untenable, and our present results support that opinion.

Summary

In 46 cases the anti-streptolysin O titre of the maternal and cord blood was estimated at the time of delivery. The level in the cord was at least twice that of the mother's in 33 cases; it was higher in 41 cases, about the same in three, and lower in only one. In one case both levels were too low to be measured.

The material for investigation was obtained through the co-operation of the obstetricians, paediatricians, and labour ward staff of Queen Charlotte's Maternity Hospital.

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NATURAL HISTORY OF CYSTIC DISEASE OF BREAST TREATED CONSERVATIVELY

BY

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Cystic disease of the breast is a common and clearly defined clinical entity. Though it has been known since the time of Réclus that the condition is potentially multiple and bilateral, much the commonest manifestation clinically is as a solitary lump in one breast, the breasts otherwise being clinically normal. If the fluid from this solitary lump is aspirated, the affected breast, after a few hours in which the site of the aspirated cyst may be felt as a hollow, becomes normal to inspection and palpation. Cystic disease of the breast has sometimes been regarded as a potentially dangerous condition with an increased liability to the development of carcinoma. The support for this view is derived less from clinical evidence than from indirect evidence in the form of histological (Cheatle, 1934–5; Willis, 1948) and animal experimental findings (Cheatle, 1934–5).

The acceptance of the view that cystic disease of the breast is a dangerous condition naturally leads to some type of excision, often simple mastectomy. While this procedure averts the postulated danger in the affected breast, it is often at the price, from the human standpoint, of a serious mutilation of the patient's womanhood, and, from the scientific standpoint, of the destruction of the clinical evidence of the subsequent natural course of the disease, which might have been innocent. Moreover, it is irrational to do a unilateral extirpation for a bilateral disease.

During the twenty-odd years that one of us (D. H. P.) has been in consultant practice he has consistently regarded cystic disease of the breast as essentially an innocent condition, to be treated preferably by aspiration. There has been one important exception to this conservative attitude. If there was any suspicion of intracystic growth—and this is easily determined if a few simple rules which will be mentioned later are followed—the condition was explored at operation and treated accordingly. The number of these cases was small, and in all of them the growth was present at the time that the patient first presented herself; in no case did it develop as a late complication in a simple cyst treated primarily by aspiration. It is argued later that these facts may warrant these cases with intracystic growth being placed in a separate group, not only from the point of view of practical management but also pathologically; and that in many cases the cyst may be a response to the growth rather than the growth being a complication of the cyst. Apart from evidence of growth in a cyst, the presence of any pathological solid lump in a breast which also contained a cyst was regarded as an indication for exploration and biopsy, as in a breast without a cyst.

In this paper the results of the above-defined conservative attitude to simple cystic disease of the breast are given. A detailed analysis can be made only of cases of cysts seen in private, because the much larger hospital group were treated as out-patients, and their records are buried in an unindexed mass of out-patient material. An attempt has been made to get over this difficulty to some extent by analysing in-patient hospital records of cases of carcinoma of the breast from the point of view of a previous history of cystic disease. The small number of cases of cystic disease with evidence of simultaneous intracystic growth are analysed separately.

Analysis of Results

Table I analyses all breast cases seen in private practice to show the relative frequency of cystic disease. The table almost certainly does not represent the true relative incidence

TABLE I.—*Diagnosis in 535 Consecutive Breast Cases Seen During 1931–50 (D. P. H.)*

Carcinoma of breast (including 5 cases of Paget's carcinoma) ..	260 cases
Painful breasts	102 ,,
Cysts of breast	76 ,,
Fibroadenoma	28 ,,
Abscess	25 ,,
Discharge from nipple	19 ,,
Miscellaneous	25 ,,

of breast conditions, owing to the unconscious selection imposed by private consultant practice. For example, painful breasts and fibroadenomata are probably much commoner than indicated, as also is the more recently defined entity known as periductal mastitis (Geschickter, 1943), or duct stagnation (Patey, 1949). But since carcinoma of the breast and cystic disease both present in a similar age group with the same symptom of a painless lump, the relative incidence of cases of carcinoma and cyst can probably be regarded as approximately accurate—that is, seven cases of carcinoma to two of cyst. It will be noted that no case has been diagnosed as chronic mastitis, which has been regarded as a non-existent disease (Patey, 1951), the postulated existence of which under this or any other name has befogged breast pathology and diagnosis for far too long.

In all 76 cases of cyst the diagnosis was proved—in 69 by aspiration and in 7 by operation. Operation was performed either because aspiration had failed, the cyst being

missed or aggregated small cysts too small to aspirate being present, or with the mistaken diagnosis of a solid lump. In all seven cases operated on, only a local excision of the cyst was carried out.

Of the 65 cases traced, to date 64 have not developed carcinoma, and one has developed carcinoma in the opposite breast. Table II gives details of these cases. The 64 cases

TABLE II.—*Follow-up of Cases of Cyst Treated by Tapping from Point of View of Development of Carcinoma*

No Carcinoma Developed After: Years	Cases	No Carcinoma Developed After: Years	Cases
16	3	7	2
15	2	6	7
14	3	5	6
13	1	4	7
12	1	3	8
11	0	2	8
10	2	1	8
9	3		
8	3		64

Carcinoma developed in opposite breast in three years in 1 case. Untraced —11 cases.

free of carcinoma have been followed up for periods varying from 1 to 16 years. The one case that developed carcinoma did so in the opposite breast three years after aspiration of a simple cyst in the first breast.

Table III gives the after-history from the point of view of the development of further cysts. It will be seen that of 55 cases treated two or more years previously on which

TABLE III.—*Follow-up of Cases of Cyst Treated by Tapping from Point of View of Recurrence of Cyst*

Total cases treated by aspiration 2 or more years ago			55 cases
Further cysts			20 ,,
No further cysts			35 ,,
—after 2 years in 5 cases		—after 9 years in 1 case	
,, 3 ,, ,, 6 ,,		,, 10 ,, ,, 1 ,,	
,, 4 ,, ,, 4 ,,		,, 12 ,, ,, 1 ,,	
,, 5 ,, ,, 3 ,,		,, 13 ,, ,, 1 ,,	
,, 6 ,, ,, 6 ,,		,, 14 ,, ,, 2 cases	
,, 7 ,, ,, 1 case		,, 15 ,, ,, 1 case	
,, 8 ,, ,, 1 ,,		,, 16 ,, ,, 2 cases	

information is available on this point, 35 have not developed further cysts and 20 have. Of the 35 cases that have not, the time that has elapsed varies from 2 to 16 years. Of the 20 cases that have developed further cysts, in 13 the further cyst or cysts were in the same breast, in two in the opposite breast, and in five in both breasts. Some further points of interest not brought out in the table may be mentioned. The first is that regular recurrences of cysts may be followed by apparent abatement. Thus, a patient had a cyst aspirated in 1942, another in the opposite breast later in the same year, and another in the first breast in 1943. From then up till the time of follow-up (1951) she had had no further trouble. Again, a patient had cysts aspirated in 1942, 1944, 1946, and 1947. From then till 1951 she had no further trouble. Secondly, large cysts do not seem particularly prone to recurrence. Thus one patient with a cyst from which 70 ml. had been aspirated had had no recurrence six years later, and another with a 120-ml. aspiration was well five years later without recurrence. One of the patients with the longest follow-up of 16 years with no recurrence of cysts had 23 ml. aspirated.

One may conclude, therefore, that, judged by the current experience over 20 years of a surgeon whose normal practice is to treat cysts of the breast by aspiration, either there is no special tendency to carcinoma or, if there is such a tendency, it requires a longer period of observation to elicit it. In the only case in which so far carcinoma has developed, since it occurred in the opposite breast to the cyst, only routine bilateral mastectomy would have prevented it; and such a drastic prophylactic procedure would require strong evidence for its justification. Apart from the question of carcinoma, the present study shows that the tendency to the development of cysts often dies out, sometimes after only one manifest cyst, at other times after a succession of cysts. Conservative treatment by aspiration is thus only a minor and often temporary burden for the patient.

The results of an analysis of the histories of 810 cases of carcinoma of the breast seen during the years 1930–50 from the point of view of a history of previous cysts are given in Table IV. These include all cases of carcinoma

TABLE IV.—*Analysis of 810 Cases of Carcinoma of Breast from Point of View of Previous Clinical History of Cysis (1930–50)*

No previous history of cyst	800
Previous history of cyst	10
(*a*) In 5 cases carcinoma in same breast as previous cyst	
(*b*) In 3 cases carcinoma in opposite breast to previous cyst	
(*c*) In 1 case carcinoma and cystic disease bilateral	
(*d*) In 1 case carcinoma unilateral and cystic disease bilateral	

Cases in which the history was of the previous removal of a lump which may have been a cyst, but in which the diagnosis was not definite, have for the purpose of this table been included in the 10 positive cases.

of the breast seen by one of us (D. H. P.) both in private practice and at the Middlesex Hospital during these years. It also includes cases of carcinoma of the breast admitted to hospital from 1930 to 1939 under a late senior colleague, Mr. Eric Pearce-Gould, who used to treat as in-patients many of the breast cases seen by one of us as out-patients, and who also was in the habit of treating simple cysts of the breast by aspiration. It will be seen from Table IV that most cases of carcinoma of the breast gave no history of previous clinical cystic disease. In the minority that did give such a history the carcinoma was only slightly more common in the breast that had been the site of the cyst clinically than in the opposite breast (5:3). Even allowing for the possibility that in some cases the history of previous aspiration was not noted, it seems clear that such a history is exceedingly rare. It can thus be concluded that, if carcinoma developed in cases of cystic disease treated conservatively as out-patients at Middlesex Hospital, the patients must have presented themselves almost exclusively to other hospitals for its treatment; and this seems a less likely conclusion than that the incidence of carcinoma was very small.

Cysts with Intracystic Tumour

As already noted, cysts with evidence of intracystic tumour have been regarded as possibly malignant and been operatively explored. Of the 886 breast cases analysed in this paper (76 cysts and 810 carcinomata) there were eight cases of cysts associated with intracystic growth (Table V).

TABLE V.—*Summary of Eight Cases Showing Carcinoma at Operation in Relation to a Cyst*

4 in association with intracystic papilloma
1 in association with aggregated multilocular cysts with intracystic papillomata
1 in wall of smooth-walled cyst
1 intracystic ?fibrosarcoma ?undifferentiated carcinoma
1 Paget's disease in opposite breast after previous mastectomy for simple intracystic papilloma in first breast

The presence of tumour in a cyst showed itself clinically in various ways. Sometimes, as in two of the eight cases, it was the tumour which was diagnosed clinically, not the cyst, the latter being noted only after amputation. In several there was a clinical history of blood-stained discharge from the nipple. But if the clinical diagnosis appeared to be simple cyst there were three features which were regarded as suspicious of intracystic tumour on aspiration and therefore warranting surgical exploration of the lump. The first was blood in the aspirated fluid, the second a persistent residual lump after aspiration, and the third a rapid—that is, within a few weeks—refilling of the cyst. We do not feel that the existence of this small and easily diagnosed group of cases of growth within a cyst of the breast ought to be allowed to prejudice the demonstrated efficiency of conservative treatment of simple cystic disease of the breast. We have recently begun the practice of getting the aspirated fluid from cysts centrifuged and examined for tumour cells, and this test should still further reduce the rare possibility of an intracystic carcinoma being missed.

Discussion and Conclusions

This paper is concerned with the natural history of cystic disease of the breast as based on clinical evidence. This does not imply any belittlement of other types of breast

study throwing light on the question, in particular histology. But, as already noted, histological evidence is often associated with an interruption of the natural history of cystic disease by a mastectomy or partial mastectomy. Only clinical evidence can be conclusive for the natural history of cystic disease of the breast as it affects the human, and it is precisely clinical evidence that has been lacking. The present paper again illustrates the time required and the difficulty experienced in obtaining conclusive clinical evidence, and it may be that a current experience of 20 years is too short a time for final conclusions. But one certainly seems justified on such current experience in tentatively concluding that, with certain simple precautions, the regarding and treating of cystic disease of the breast as an innocent condition has not up to the present been shown to be fallacious by the frequency of development of carcinoma.

The criticism might possibly be made that, from the point of view of the liability of cystic disease to carcinoma, the eight cases with associated intracystic growth ought not to be treated as a separate group, but ought to be grouped with the one case of cystic disease treated by aspiration in which subsequent carcinoma did develop. But in reply it should be emphasized that in all these eight cases it was not a question of a tumour developing as a complication in a previously known cyst treated conservatively, but of eight patients who at their first attendance had tumours of the breast which happened to be associated with cysts, often not diagnosed clinically. There was no definite evidence in any of them that the cysts preceded the tumours, and in most it was at any rate equally probable that the reverse process occurred and that the tumours preceded the cysts. Certainly in the commonest group—the intracystic papillomata (five cases)—the cysts were probably due to distension of the associated duct with the blood shed by the papillomata, a process that in lesser degree is recognized as a common occurrence in the small intraduct papillomata in the ducts near the nipple.

We feel, therefore, that many of these cases belong to a separate group pathologically as well as being clearly recognizable as a separate entity clinically, and that part of the confusion in the past about the relation of cystic disease of the breast to carcinoma has arisen through wrongly grouping together two separate types of condition. Finally, since carcinoma and cystic disease are both common conditions, it must occasionally happen that the two will present clinically at the same time. The treatment of these cases is of course the treatment of the carcinoma, but it would be wrong to assume from simultaneous presentation a necessarily causal relation between the two conditions. This study therefore furnishes support for the view that cystic disease of the breast can with simple precautions be treated conservatively. It also furnishes support for the efficacy of the simplest form of conservative treatment—aspiration.

Summary

Of 76 cases of cyst of the breast treated conservatively, 65 of which have been followed for from 1 to 16 years, only one is known to have developed carcinoma, and that in the opposite breast.

Aspiration of a cyst is not necessarily followed by the development of further cysts, and, if it is, the tendency to cyst formation may disappear.

Of 810 cases of carcinoma of the breast only 10 had a previous clinical history of cyst.

In a further eight of these cases growth developed apparently simultaneously with and in relation to a cyst, but this group of cases readily lends itself to recognition clinically, and is probably a separate group pathologically.

With simple precautions, conservative treatment by aspiration is an efficient and safe treatment for cystic disease of the breast.

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A.C.T.H. IN DIAGNOSIS OF ADRENAL INSUFFICIENCY (THORN TEST)

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In 1948 Forsham *et al.* investigated the metabolic and haematological response of human subjects to a single dose of 25 mg. A.C.T.H. They compared the response of 30 patients with Addison's disease with that of 10 normal subjects and 40 hospital patients with presumably intact adrenal cortical function. They found a mean fall of 74% in the number of circulating eosinophils in the individuals with normal adrenal cortical function, and a mean fall of only 4% in the patients with Addison's disease.

The fall in the eosinophil count was accompanied by a mean increase in the urinary uric-acid/creatinine ratio of 87% in the control series and of only 16% in the cases of Addison's disease. Both changes were maximal four hours after the injection of A.C.T.H. A normal eosinophil response, and at the same time an increase of 48% in the uric-acid/creatinine ratio, could, however, be elicited in patients with Addison's disease after they were given 20 mg. of 17-hydroxycorticosterone (compound F), suggesting that the response to A.C.T.H. was mediated by an increase in secretion of 11-oxysteroid compounds by the adrenal cortex. On the basis of these observations Forsham *et al.* devised a "four-hour test" of adrenal cortical function.

In a later article Thorn *et al.* (1951) reported a larger series of similar observations. In 50 cases of Addison's disease there was an average fall of only 7% in the eosinophil count, and in about one-third of the cases there was actually an increase. Patients with hypopituitarism showed an average fall of 31%, the magnitude of the change depending upon the degree and duration of adrenal cortical involution.

Thorn and his colleagues also introduced a 48-hour test, in which changes in the eosinophil count and in the urinary 17-ketosteroid excretion were measured, in response to the intramuscular administration of A.C.T.H. in divided doses over a period of 48 hours (Thorn and Forsham, 1949; Roche, Forsham, Forsham, and Thorn, 1950; Thorn *et al.*, 1951). This test was carried out in 100 subjects. In 35 patients with normal adrenal cortical function the eosinophil count fell by 77% after 48 hours; the urinary 17-ketosteroid excretion increased by an average of 10.1 mg. per 24 hours in 15 normal male subjects and of 7.2 mg. per 24 hours in 20 normal female subjects, whereas there was no significant change in patients with Addison's disease. In most cases of hypo-

pituitarism the eosinophil counts and the urinary 17-ketosteroid levels responded normally in the 48-hour test, but they did not do so in the four-hour test. Thorn and his colleagues therefore claimed that a 48-hour test was of value in distinguishing adrenal failure secondary to hypopituitarism from primary adrenal failure.

More recently Renold *et al.* (1951) reported that the intravenous infusion of 20 mg. of A.C.T.H. in saline over a period of 8 to 24 hours produced a marked adrenal cortical response, which was comparable to that obtained by the intramuscular injection of five to ten times this amount in six-hourly doses over a period of 24 hours. Administration of the same dose intravenously in the course of one minute did not produce any measurable response, and larger doses did not appear to increase the response in four patients who had become resistant to the hormone after intramuscular administration. There was still no response in cases of Addison's disease. No anaphylactic reactions were seen in over 100 patients.

Recant *et al.* (1950) introduced a four-hour adrenaline test. A subcutaneous injection of 0.3 mg. of adrenaline failed to induce a fall in the eosinophil count of 50% or more in 30 out of 34 cases of Addison's disease. By increasing the dose of adrenaline to 1.5 mg. and giving it in saline intravenously over a period of one hour they obtained a fall in the eosinophil count of up to 50% or more in patients with Addison's disease. The adrenaline test showed a greater impairment of response than did the A.C.T.H. test in cases of hypopituitarism. It was suggested that this was due to interruption of the hypothalamic-pituitary pathway; it is thought that adrenaline normally exerts its effect upon the adrenal cortex through this pathway, although it also acts directly upon the adrenal cortex itself, as shown in mice and rats (Long and Fry, 1945; Recant *et al.*, 1948; Speirs and Meyer, 1949). The normal response obtained in some cases of Addison's disease, in spite of the failure of response to A.C.T.H., suggested that endogenous secretion of A.C.T.H. had been stimulated and that remnants of adrenal cortical tissue had consequently become activated.

Material and Methods

The following is an account of the application of the Thorn test with A.C.T.H. to eight classical cases of Addison's disease, in six of which at least one crisis had occurred, to four cases of post-partum panhypopituitarism (Simmonds's disease), and to seven cases in which a diagnosis of adrenal insufficiency had been considered but not established. The four-hour test was used in all cases, except in two cases of Simmonds's disease; in one of these the 48-hour intramuscular test was performed, while in the other the intravenous test was employed.

Seven of the eight cases of Addison's disease were already under treatment with implantations of 300 mg. of D.C.A. (deoxycortone acetate) every six months. In each case the Thorn test was carried out six months after the last implant, by which time it was assumed that the effects of the D.C.A. had to a large extent worn off.

Procedures

1. *The Four-hour Test.*—The patient was allowed no food after 8 p.m. on the day before the test. On the following day the bladder was emptied and the urine discarded at 6 a.m. The patient then drank 200 ml. of water. The bladder was emptied again at 10 a.m. and the urine was kept for estimation of the uric acid and creatinine concentrations (the "pre-treatment" specimen). A chamber eosinophil count was also performed at 10 a.m., and immediately afterwards 25 mg. of A.C.T.H. was injected intramuscularly. A further 200 ml. of water was drunk, and at 11 a.m. the bladder was emptied again and the urine discarded. At 12 noon the patient drank a final 200 ml. of water. The bladder was emptied once again at 2 p.m., and this specimen was kept for estimation of uric acid and creatinine concentrations (the "post-treatment" specimen). A second chamber eosinophil count was also performed at 2 p.m.

Interpretation: a fall in the eosinophil count with a rise in the uric-acid creatinine ratio, each exceeding 50%, is regarded by Forsham *et al.* (1948) as indicating normal adrenal cortical reserve, whereas in the presence of Addison's disease the fall in eosinophil count is usually less than 20%.

2. *The 48-hour Intramuscular Test.*—Urine was collected throughout the 24 hours immediately preceding the test, and the whole amount was saved for estimation of the 17-ketosteroid level. On the morning of the test an eosinophil count was made. A.C.T.H., 25 mg., was then given immediately by intramuscular injection, followed by 10 mg. intramuscularly every six hours until 48 hours after the first injection. A further eosinophil count was made four hours after the last injection, and during the next 24 hours urine was collected again for another estimation of the 17-ketosteroid level. The patient was not in a fasting state during the test.

3. *The Intravenous Test.*—Urine was collected throughout the 24 hours immediately preceding the test and the whole amount was saved for estimation of the 17-ketosteroid level. After an initial eosinophil count an intravenous infusion of normal saline was set up containing the equivalent of 40 mg. of LA-1-a A.C.T.H. This amount was administered over a period of 18 hours. Two hours after the infusion was completed a further eosinophil count was performed, and during the next 24 hours the urine was again collected for estimation of the 17-ketosteroid level. The patient was not in a fasting state during the test.

The chamber eosinophil counts were performed by the eosin–acetone method of Forsham *et al.* (1948) in most cases. More recently, the method of MacFarlane and Cecil (1951) has been used.

The urinary uric acid and creatinine concentrations were estimated by the method of Folin (1914), and the 17-ketosteroid excretion by the method of Greenburgh *et al.* (1950), a modification of the method of Tompsett and Oastler (1946).

Results

Six of the eight proved cases of Addison's disease showed a fall in the eosinophil count of less than 50%; in five cases the fall was less than 20%. In the other two cases, however, the number of circulating eosinophils fell by 57% and 75% respectively (see Table). One of these (Case 7) was one of the most severe cases of Addison's disease in the whole series; this patient has been admitted to hospital in crisis or impending crisis on six occasions. The other patient (Case 8) was thought, on clinical grounds, to be recovering at the time at which the Thorn test was performed, but she died a fortnight later from a severe respiratory infection; at necropsy no trace of adrenal cortical tissue could be found even on histological examination, and there was generalized hypertrophy of lymphoid tissue and of the thymus.

Each of the four cases of panhypopituitarism showed a fall in the number of eosinophils of less than 50%. In one of these cases the 48-hour test was carried out; in another the intravenous test was used.

The initial eosinophil count varied between 50 and 800 (average 220) per c.mm. in the proved cases of Addison's disease, between 100 and 1,100 (average 482) per c.mm. in the cases of panhypopituitarism, and between 10 and 270 (average 121) per c.mm. in the cases in which a diagnosis of Addison's disease was not substantiated.

The percentage fall in the eosinophil count ranged from 0 to 75% (average 22%) in the proved cases of Addison's disease, from 9 to 39% in the cases of panhypopituitarism, and from 0 to 92% (average 49%) in the cases in which the diagnosis of Addison's disease was thought to be unlikely.

The changes in urinary uric-acid/creatinine ratio seemed to bear no relation to the changes in eosinophil count. In fact, only two patients in the whole series showed a rise of uric-acid/creatinine ratio of more than 50%. Both were known to be suffering from Addison's disease; one of them also showed a normal eosinophil response.

In Case 12 the urinary 17-ketosteroid figure rose from 2.1 to 5.4 mg. per 24 hours after the administration of A.C.T.H. by intravenous infusion over a period of 18 hours.

Significance of Eosinophil Counts

There are several possible limitations of the use of eosinophil counts as an index of adrenal cortical function.

1. The test assumes that spontaneous fluctuations of the eosinophil count of more than 50% do not occur under normal conditions. The evidence on this point is conflicting. Hills *et al.* (1948) state that significant fluctuations were not observed in normal subjects, under basal conditions, and without the administration of A.C.T.H. Recant *et al.* (1950) found that the diurnal variation in the eosinophil count of six young adult males, under constant conditions in hospital, did not exceed 40% of the initial levels; the number of eosinophils usually rose gradually during the course of the afternoon. Kellgren and Janus (1951) found that in four healthy male subjects, under normal conditions, the eosinophil counts varied by up to 300% on different days in any one subject, but that the mean fluctuation in counts performed at two-hourly intervals on the same day was no more than 10% of the morning count in any one subject; there was, however, an occasional increase or decrease of about 40%. Abelson and Moyes (1950) found eosinophil counts ranging from +13% to −30% of the initial level in 13 patients with pulmonary tuberculosis under basal conditions.

Most other workers, however, have found considerable diurnal fluctuations in the eosinophil count under normal conditions. Rud (1947) found a marked fluctuation, even from minute to minute, and a typical rhythmical variation during the course of 24 hours. There was a decrease in the early morning hours, with a minimum count between about 9 and 11 a.m., followed by a rise, reaching a peak between noon and 1 p.m., and a maximum level at 5 p.m. He suggested that four counts should be made at intervals of 15 minutes on the afternoons of five or six successive days, and that an average should be taken of all these counts. Herbert and de Vries (1949) found diurnal variations of from 30% to 66% in four subjects under normal conditions. Broch and Haugen (1950) found marked variations under standard conditions and regarded a deviation of 50% as being within the normal range.

Fisher and Fisher (1951) performed 463 counts upon 170 normal persons. Of these, 238 were made on subjects who had been fasting for periods of 12 to 16 hours and 225 were made in a non-fasting state. Of the counts on fasting subjects 23% dropped by 40% or more between 8 a.m. and 12 noon and 11.6% fell by 50% or more; the variations ranged from a fall of 76% to a rise of 165.4%. About one-third of the counts remained the same and 7.3% rose by 50% or more. Only 13% of the non-fasting group showed a decrease of 40% or more between 8 and 11 a.m., but 9.3% dropped by 50% or more. The percentage fall between 11 a.m. and 3 p.m. was less: only 5.3% showed a fall of 50% or more. Over the whole period from 8 a.m. to 3 p.m., 18.6% of the counts fell by 40% or more, 13.3% fell by 50% or more, and 8% rose by 50% or more.

Swanson *et al.* (1952) studied the diurnal variation of eosinophil counts in five healthy subjects during their daily work, and in five patients with rheumatoid arthritis and three with ankylosing spondylitis under normal in-patient conditions. They found a diurnal variation similar to that observed by Rud (1947)—namely, a high early morning count, falling until about midday, followed by a slight rise, another fall in the early afternoon and a further rise towards evening. In the morning a spontaneous fall of more than 50% in the number of eosinophils occurred eight times (in 4 of the 13 subjects), usually within three to four hours. In the afternoon the fall was greater than 40% in only one case; the drop was complete within two hours, and was offset by a greater rise later on. The overall change during the course of the day varied from a fall of 55% to a rise of 128.6%, as compared with a range of −70% to +262% found by Rud in 53 series of counts in 41 subjects.

Swanson *et al.* therefore conclude that one should be cautious in attributing a fall in the eosinophil count to the administration of A.C.T.H. if a Thorn test is carried out during the morning, while a drop of more than 40% during the afternoon is more likely to be significant, especially if it lasts for more than two hours. They criticized the findings of Recant *et al.* (1950) and of Abelson and Moyes (1950) on the grounds that their counts were made at two-hourly intervals only, and that fluctuations might have escaped detection, since the maximum morning fall often took place at the third hour in their own series.

Forsham *et al.* (1948) originally stipulated that the A.C.T.H. test should be performed in the morning, with the patient in a fasting state. Roche, Thorn, and Hills (1950), however, allowed breakfast to be taken before the test, and Swanson *et al.* (1952) found that the midday rise and fall in eosinophil count bore no relation to meals, and that instead of a larger fall occurring after lunch than after breakfast the opposite was true. In one case they found that the midday change in the number of eosinophils still occurred during a one-day fast, though Rud observed that the count usually fell during the afternoon as a result of fasting, instead of rising, as in normal conditions. Swanson *et al.* showed that waking had a more important effect than food upon the eosinophil count, and that the morning fall occurred earlier in hospital patients, who woke earlier; but Rud found no evidence that either food or sleep *per se* markedly influenced the variations in the count, which he regarded as "relatively autonomous."

2. The technique of eosinophil counting may be subject to considerable errors, as may any chamber cell count. Some workers have used modifications of Dunger's (1910) method. Rud (1947) used a magdala-red stain in acetone, and Forsham *et al.* (1948) an eosin-acetone preparation as diluent. Randolph (1944) found that the cells rapidly became lysed by this diluent and introduced phloxine and propylene glycol instead, which, he claimed, overcame these disadvantages and made identification of cells easier. Henneman *et al.* (1949) confirmed his findings, and Swanson *et al.* (1952) obtained consistent results, using Randolph's method, either on venous or on capillary blood. The eosin–acetone method of Forsham *et al.* (1948) was originally used in our cases, but later MacFarlane and Cecil's (1951) modification of Pilot's method, using a phloxine and propylene glycol diluent, was adopted. Both methods have given comparable results, but the method of Forsham *et al.* has the disadvantage that the cells are lysed unless the count is carried out immediately.

3. The initial eosinophil count in the Thorn test may be so low that the significance of a fall in the number of cells after the administration of A.C.T.H. may be difficult to assess, even if it is expressed as a percentage of the initial figure. Thus the initial counts in two of our cases of Addison's disease were 50 and 70 per c.mm., and in three of the cases in which adrenal insufficiency was not confirmed they were as low as 10, 40, and 80 per c.mm. In one of the two severe cases of Addison's disease which showed a fall in eosinophil count of more than 50%, the count was 70 per c.mm. before A.C.T.H. was given and 30 per c.mm. afterwards; though this represents a drop of 57%, the change appears unconvincing when expressed in absolute figures.

4. The fact that the eosinophil count can fluctuate by more than 50% in cases of Addison's disease severely limits its value in the diagnosis of adrenal insufficiency. It is quite possible that the fall in the number of cells in two of our cases of Addison's disease was independent of the administration of A.C.T.H. Although Thorn and his colleagues did not find a significant eosinophil response to the administration of A.C.T.H. in any of their cases of Addison's disease, they do mention a few cases in which a fall of more than 50% in the number of eosinophils was obtained in response to the administration of adrenaline, suggesting that sufficient remnants of adrenal cortical tissue may survive to give this response. Recant *et al.* (1950) also point out that in rare

instances of dissociation of adrenal cortical function there may be adequate secretion of 11-oxysteroid compounds, in spite of deficiency of other steroids; in such cases the eosinophil response will not reflect the whole adrenal cortical reserve.

5. Forsham *et al.* (1948) and Thorn *et al.* (1951) point out another limitation to the test—namely, that in rare cases A.C.T.H. given at the height of an acute allergic eosinophilia may fail to reduce the number of eosinophils. In such a case, they state that if 50 mg. of cortisone given by mouth (or 50 ml. of aqueous adrenal cortical extract given by injection) produces a fall in the eosinophil count of 50% or more, adrenal insufficiency is indicated rather than a refractory eosinophilia.

It might be expected that the eosinophil count should be higher in the presence of adrenal insufficiency than in normal subjects. Our series of cases is too small to allow any definite statement on this point, but only one case of Addison's disease and one case of hypopituitarism showed high counts (800 and 1,100 per c.mm. respectively). Forsham *et al.* found no difference between the initial counts in patients with Addison's disease and those of control subjects, though the counts varied widely as between different individuals.

Significance of Changes in the Urinary Uric-acid/creatinine Ratio

Forsham *et al.* stated that the urinary uric-acid/creatinine ratio remained remarkably constant from day to day, and that the increase in the ratio was mainly due to a rise of uric acid excretion, the urinary creatinine concentration usually remaining unchanged or diminished. They found, however, that the difference between the response to A.C.T.H. of normal individuals and that of patients with Addison's disease was not as clear-cut as the difference in eosinophil response. In the series reported here the changes in uric-acid/creatinine ratio seem to bear no relation to the changes in eosinophil counts. In fact, only 2 patients out of the 16 tested showed a rise of uric-acid/creatinine ratio of more than 50%. Both were known to be suffering from Addison's disease; one of them also showed a normal eosinophil response (see Table).

Forsham *et al.* pointed out certain limitations of the uric acid excretion as an indicator of reactivity to A.C.T.H. (1) Uric acid clearance may be nearly maximal in cases of dehydration, gout, leukaemia, or renal insufficiency, and a further increase may be impossible. (2) In patients with severe liver damage the formation of uric acid from its precursors may be impaired, thus limiting the rise in uric acid concentration in the blood and urine in response to A.C.T.H. (3) Reduction in the rate of breakdown of uric acid, as in hypothyroidism, might limit the response to A.C.T.H.

In Case 15 of this series there was tuberculous disease of the kidney, and in Case 19 the patient was suffering from chronic nephritis, so that renal disease probably vitiated this part of the test. In Case 16 the fluid and electrolyte balance was so deranged and the patient so uncooperative that an estimation of the uric-acid/creatinine ratio was impracticable.

Broch and Haugen (1950) found a great variation in the urinary uric-acid/creatinine ratio under standard conditions, and regarded a deviation of 50% as within the normal range.

Taussky *et al.* (1951) also pointed out the limitations of changes in the uric-acid/creatinine ratio as an index of adrenal cortical function. They found that fasting, by itself, led to a considerable rise in the ratio in normal subjects. This rise was not generally as pronounced as that which followed the administration of A.C.T.H., but it could account for an appreciable part of it. In contrast, the eosinophil count did not vary significantly with starvation alone. The degree of increase in the uric-acid/creatinine ratio, after fasting or after administration of A.C.T.H., seemed to vary inversely with the level of uric acid excretion during the control period, the latter being influenced by the purine content of the diet.

Thorn *et al.* (1951) have therefore abandoned the estimation of the uric-acid/creatinine ratio in testing for adrenal responsiveness.

Discussion

Although the series recorded here is a small one, it contains enough evidence to suggest that the Thorn test does not give an entirely reliable indication of adrenal cortical function. A normal eosinophil response to a single injection of 25 mg. of A.C.T.H. was obtained in two patients (Cases 7 and 8) with severe Addison's disease, one of whom died shortly afterwards and showed no trace of adrenal cortical tissue at necropsy. A normal eosinophil response does not therefore rule out the diagnosis of Addison's disease, though it would be dangerous to ignore a response of less than 50% in a doubtful case. In Case 14, for instance, the diagnosis of Addison's disease was in considerable doubt, and the eosinophils fell by 69%; in view of the findings in Cases 7 and 8 Addison's disease could not be excluded by the Thorn test alone. In Case 13 the diagnosis of Addison's disease had more to support it on

Table of Results of Thorn Test

Case No.	Diagnosis	Eosinophils/c.mm.		Urine (Initial)			Urine (4 Hours after A.C.T.H.)			% Change of Eosinophils	% Change of U-a/C. Ratio
		Initial	4 hrs. after A.C.T.H.	Uric Acid mg./100 ml.	Creatinine mg./100 ml.	Uric-acid/ Creatinine Ratio	Uric Acid mg./100 ml.	Creatinine mg./100 ml.	Uric-acid/ Creatinine Ratio		
1	Addison's disease	280	260	60	80	0·75:1	91	92	0·99:1	−7%	+32%
2	" "	200	160	55·8	115	0·49:1	80	124	0·64:1	−20%	+31%
3	" "	250	230	40	147	0·27:1	33·7	134	0·25:1	−8%	−7%
4	" "	200	200	12	108	0·11:1	16	132	0·12:1	No fall	+9%
5	" "	50	55	10·3	35	0·29:1	42·5	81	0·52:1	"	+79%
6	" "	800	750	10·3	89	0·11:1	8	70	0·11:1	−6%	+9%
7	" "	70	30	32	124	0·25:1	42	109	0·39:1	−57%	+56%
8	" "	120	30	72·8	128	0·57:1	62·5	144	0·44:1	−75%	−23%
9	Panhypopituitarism	450	320	33·6	101	0·33:1	24·6	83	0·3:1	−23%	No increase
10	"	1,100	1,000	38·1	112	0·33:1	115	45·5	0·4:1	−9%	+21%
11	"	160 to 100 (over 24 hours)	80 (no further change after 48 hours)	—	—	—	—	—	—	−20%	—
12	"	280	170 (after I.v. infusion for 18 hours)	—	—	—	—	—	—	−39%	—
13	?Addison's disease	270	160	38	80	0·47:1	56	93	0·6:1	−41%	+28%
14	" "	80	25	122	124	0·98:1	92·5	116	0·8:1	−69%	−18%
15	Renal tuberculosis	140	10	41	88	0·465:1	46	95	0·48:1	−92%	+3%
16	Anorexia nervosa	10	25	—	—	—	—	—	—	No fall	—
17	"	200	150	64	294	0·22:1	36	150	0·24:1	−25%	+9%
18	Anxiety state	40	20	38	120	0·32:1	42	97	0·435:1	−50%	+36%
19	Chronic nephritis	110	40	13·9	55	0·25:1	12·7	51	0·25:1	−64%	No change

clinical grounds, and there was only a 41% fall in the number of eosinophils; this is suggestive evidence of adrenal insufficiency, but enough time has not yet elapsed to enable the diagnosis in the case to be confirmed by a therapeutic test with D.C.A. In Case 17 there was no real evidence of adrenal insufficiency; yet the eosinophil count fell by only 25% after the administration of A.C.T.H.

While the diagnosis of Addison's disease may present no great problem in severe cases with classical pigmentation, hypotension, and crises, in a number of cases the blood pressure and blood chemistry are normal, pigmentation is atypical, and crises have not occurred. In the latter type of case the only clinical evidence for the diagnosis may be a combination of slight pigmentation, asthenia, and gastro-intestinal disturbance. Laboratory tests may be negative and there may be no calcification of the adrenal glands. The urinary 17-ketosteroid level may be reduced, but this is less helpful in the male in view of the testicular component. The Robinson–Power–Kepler test (1941) is perhaps the most helpful, but false positive results may be obtained in a number of conditions other than adrenal insufficiency (Levy *et al.*, 1946).

It is evident that there is still no single diagnostic test for Addison's disease which is completely reliable, and that, while a combination of the various tests may often be helpful, the diagnosis must in the last resort be made on clinical grounds.

Summary

The response of the eosinophil count and the uric-acid/creatinine ratio to the administration of A.C.T.H. was estimated in eight proved cases of Addison's disease, four cases of panhypopituitarism, and seven cases in which a diagnosis of adrenal insufficiency had been considered but not established.

Six of the eight patients with Addison's disease showed a fall of less than 50% in the eosinophil count. The other two showed falls of 57% and 75%, though in the former case the initial count was comparatively low and the change may not have been significant. Both these patients were suffering from a severe form of the disease, and the second of them died a fortnight after the test as a result of a severe respiratory infection; at necropsy no trace of adrenal cortical tissue could be found. In each of the four patients with hypopituitarism the eosinophil count fell by less than 50%. In the third group of cases four out of seven showed a normal eosinophil response; the other three showed subnormal responses, but one of them may prove to be a case of Addison's disease.

A number of workers have shown that the eosinophil count may fluctuate widely during the course of the day, and that the changes may exceed 50% of the initial level. Thus a fall in the eosinophil count exceeding 50% after the administration of A.C.T.H. does not exclude adrenal insufficiency, though a fall of less than 50% is strongly suggestive of such a diagnosis.

Changes in the uric-acid/creatinine ratio are of no value as an index of adrenal responsiveness.

The Thorn test is a useful addition to existing diagnostic methods, but it is subject to the limitations common to most laboratory tests, and the diagnosis must still, in the last resort, be made on clinical grounds.

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TOXIC REACTIONS DUE TO INTRAVENOUS IRON

BY

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The work of Nissim (1947) and Wilkinson and Slack (1949) on intravenous iron needs no introduction. Although its therapeutic value is undisputed, iron is nevertheless a dangerous drug. The dangers of its oral use, especially in children, are well known. That it can cause reactions intravenously is also becoming increasingly obvious. These are usually mild, but severe ones have been reported (Govan and Scott, 1949; Mooney, 1950; Slowik, 1950; Ramsey, 1950; Birch and Till, 1951). Two further cases are here recorded and discussed.

Case 1

A housewife aged 24 was admitted on November 22, 1950, with chronic pulmonary tuberculosis. This started in 1945, and had recently been complicated by amyloid disease manifested by massive albuminuria. On December 6 the haemoglobin was 40%, plasma proteins 7.2 g. (albumin 1.1 g., globulin 6.1 g.). A course of oral iron (tab. ferr. sulph. co.) was given, with poor response. On December 18 intravenous therapy was begun. "Ferrivenin," 100 mg. (5 ml.), was injected on December 18, 22, and 27. Within one minute of the last injection an epileptiform fit occurred, lasting four minutes. On recovering, the patient said her eyes became blurred after the injection, but she remembered nothing else. She afterwards complained of lumbar pain lasting 30 minutes, then pain in the chest for 24 hours.

On January 10, 1951, her haemoglobin was 72%. On February 9 a different preparation, "neo-ferrum," was used intravenously, 100 mg. (5 ml.) being injected slowly. A few seconds later she complained of a burning sensation at the

site of the injection, soon spreading to the head and neck, which flushed deeply. Shortly afterwards she complained of lumbar pain lasting a few minutes, followed again by a feeling of warmth and flushing. Some hours later she complained of pain in the left shoulder, heat, and sweating. Next day she was normal. On February 13 the haemoglobin was 76%, plasma proteins 7.3 g. (albumin 2.8 g., globulin 4.5 g.). There was still albuminuria. Later she had a three-stage thoracoplasty. Her haemoglobin was still 76%.

Case 2

A female hairdresser aged 24 was admitted on January 13, 1951, with acute tuberculous laryngitis and bronchopneumonia. There was a long history of "asthma." She was treated with "sterazol" and oral iron, and, although her tuberculous condition improved, her haemoglobin fell to 40%, plasma proteins being 7.5 g. Intravenous iron, using neo-ferrum, was therefore begun in mid-February; two doses of 100 mg. (5 ml.) were well tolerated. On March 2 a third dose of 100 mg. was given. Two minutes later she complained of severe pain in the head and thought she was dying. Severe dyspnoea and cyanosis supervened and the pulse became imperceptible. Adrenaline 1:1,000, 15 min. (0.9 ml.), was given immediately; five minutes later she felt better, although very "wheezy." Since admission she had complained of intermittent wheezy attacks relieved by ephedrine, adrenaline, and isoprenaline.

In view of the severe reactions, 1 dr. (3.5 ml.) of neo-ferrum thrice daily, orally, was substituted when the haemoglobin was 60%, with poor results. On April 4 it was decided to try intravenous therapy again, using very small doses of ferrivenin. On July 13 5 mg. (0.25 ml.) was given, but one and a half hours later she felt a slight constriction of the chest, which lasted all day. Further doses of 10 mg., 20 mg., and 40 mg. were given without ill effect. On July 23 80 mg. was given, and one hour later she went pale, then flushed, felt faint, and complained of tightness of the chest and dyspnoea, the whole lasting for a few minutes. Three further doses of 60 mg. were given without ill effect. On August 1 the haemoglobin was 63%. On August 3 70 mg. was given; this was followed one minute later by wheeziness and dyspnoea lasting two hours. On the 7th 65 mg. was followed in seven hours by faintness, and by pain in the limbs lasting 12 hours. Further doses of 62.5 mg. and 65 mg. were well tolerated. On August 14 67.5 mg. produced a slight wheeze after one minute, followed by faintness and headache for eight hours. Two further doses of 65 mg. were well tolerated, a third dose of 65 mg. being followed by a transient wheeziness and dyspnoea. A few further doses of 65 mg. were again tolerated.

On August 27 her haemoglobin was 70%. She now had had an eight-months course of sterazol with great clinical improvement in lungs and larynx. It was therefore stopped, and, although the possibility of drug haemolysis had been considered for some time, it was felt that, in view of her hopeless state on admission, both drugs should be persisted with. However, on November 27 oral iron was again substituted, and on December 12 her haemoglobin was 81%. During the whole period of treatment she still complained of intermittent wheezy attacks, relieved by adrenaline.

Discussion

The problem of intravenous iron intoxication may be approached in two ways: (1) the transport of iron in the blood; and (2) allergy. The intravenous method differs from the oral one in that the factors of local gastro-intestinal irritation and absorption are eliminated.

Transport of Iron in the Blood

Iron is directly introduced into the general circulation, and its attendant reactions must be intimately bound up with the question of transport in the blood itself. Laurell (1947) considers this to be closely associated with the binding capacity of the plasma proteins, especially the β-globulin-fraction iv-4(8) of Cohn *et al.* (1946). He introduced the term "saturation limit" for measuring the capacity of serum for firm binding of iron, including both the native iron content and that introduced therapeutically. Serum binds this iron content up to the saturation limit, which is not exceeded or influenced by the ingestion of large amounts of iron. The quotient manifest/latent iron-binding capacity of serum appears to vary regularly with changes in intermediary iron metabolism, and it seems probable that this iron-binding component of serum serves as a regulation of iron exchange between the various organs. After intravenous injection the value of serum iron is high, but in the presence of the normal saturation limit the latent iron-binding capacity is low. In chronic infection—for example, tuberculosis—however, the saturation limit is lowered too.

The unsaturated capacity of Cohn's globulin fraction to bind iron is roughly two to three times the normal level of serum iron (Klopper, 1951). Using rough calculations of plasma volume, he thinks that toxic effects arise only when the iron-binding capacity is exceeded in the individual injection. As Govan and Scott (1951) point out, reactions depend on the amount given in a single injection. In Case 2, although there appeared to be a critical level (65 mg. or more) above which a reaction was likely to occur, nevertheless a difference of as small an amount as 0.5 mg. between a reacting and a non-reacting dose seemed to be well tolerated. Klopper (1951) also thinks that complex saccharated iron compounds give up their molecular iron more slowly to the serum proteins than do simple iron salts. The rate of dissociation may well vary with the amount of globulin available at any given time. Case 2 was a known asthmatic. Altered tissue-protein relationships are well known to occur in this condition, but whether they can influence the amount of available globulin is conjectural.

The level of serum iron and the percentage saturation of iron-binding proteins are carefully regulated. Conditions in which the latter is increased include iron excess, bone-marrow block, and severe liver disease. The role of the liver is important because it is the chief iron-storage depot in the body. Depression of percentage saturation occurs in iron deficiency and in infections. Case 1 almost certainly had amyloid disease of the liver, and both cases were anaemic. Iron saturation and transport were therefore severely affected. Rath and Finch (1949) do not accept Laurell's hypothesis that the *degree* of saturation regulates iron absorption, for the injection of iron-binding protein exerts only a very temporary effect on the serum-iron level. It remains to be seen how much one may aid or interfere with iron transport by increasing or decreasing the amount of iron-binding protein.

It is well known that absorption of iron from the alimentary tract occurs by oxidation of the substance apoferritin to the crystallizable protein ferritin. In the blood stream the iron becomes detached from ferritin and is taken up by siderophillin, which may be the same as Cohn's globulin fraction, for transport. The rate at which ferritin releases its iron depends not on the level of serum iron but on the level of blood oxygen. Rapid transport therefore occurs only if the oxygen level is low, as in anaemia. If a similar method of take-up be postulated after intravenous therapy, the rate of take-up in both these patients who were severely anaemic may have been quickened. Andersson (1950), using rabbits, had to give 10 times the therapeutic dose before toxic reactions appeared. The factor of anaemia may explain the rapid onset of symptoms.

Allergy

The question of allergy seems to me to be important. Landsteiner (1924) showed, in guinea-pigs, that it is possible to make animals hypersensitive against a single chemical

group, such as *para*-arsanilic acid, by combining it with different proteins—for example, animals could be sensitized by injection of one azoprotein combined with diazotized *para*-arsanilic acid against another compound containing the same azo-component but a different protein. The animals did *not* react to compounds uncombined with protein. It would seem that the simple compounds mentioned are fixed by the cells in which the anaphylactic reaction occurs. This could be the mechanism causing the reactions to oral and intravenous iron, for, as has been discussed above, iron transport seems to depend on an iron–protein complex, and this protein component could well account for the anaphylactic phenomena such as were seen in Case 2—pallor, wheeziness, cough, and so on.

Sinclair and Duthie (1949) also describe a case in which 200 mg. caused flushing of the face and transient bronchospasm, but 100 mg. did not, nor did a further dose of 200 mg. In other words, by using graduated doses, one presumably gradually increases the amount of iron-binding protein used per injection. It is not the iron itself, therefore, but the protein complex which acts as a desensitizing agent (cf. pollen-allergy, etc.). Ramsey (1950) has described symptoms of nausea, vomiting, flushing, and shock after using single large doses of up to 900 mg. Some of these reactions occurred five hours after injection. He thought these late reactions resembled those due to cold haemoglobinuria, and that they were due to increased reticuloendothelial activity. I feel that they resemble serum reactions—for example, antidiphtherial, antistreptococcal, etc. —and could be equally well ascribed to the same allergic causes. Although massive doses of antidiphtheria serum—for example, 100,000 units—can cause anaphylaxis, as little as 0.2 ml. of antiscarlatinal serum has also been responsible.

Beaumont and Dodds (1952) think that a long interval between injections predisposes to toxic phenomena, and quote the case of Govan and Scott (1949), in which a severe reaction with faintness, giddiness, vomiting, and slow pulse occurred, there being an interval of 12 days between the preceding and the toxic doses. I feel, however, that again this is more in keeping with an anaphylactic reaction.

Vaughan (1948) suggests that the anaemia of trauma and sepsis is dependent on a disturbance of haemoglobin synthesis, especially the globin element, this being, in turn, part of a wider disturbance of protein metabolism dependent on the action of breakdown products liberated from injured tissues or by the need of injured tissues for special amino-acids. In long-standing pulmonary tuberculosis, disturbance of protein metabolism occurs, as has been mentioned above. This special factor might well influence the tendency to iron reactions in tuberculous subjects.

Cartwright *et al.* (1946) showed that, in infection, iron injected intravenously was removed from the blood rapidly until the infection was controlled. Greenberg *et al.* (1947) also showed that major deviation occurred to the normal storage areas, especially the liver, because the iron cannot be used to form haemoglobin, the plasma excess being diverted as a protection against toxic effects. The use of large doses of intravenous iron, therefore, in subjects with chronic infective states such as tuberculosis may predispose to such effects, although the mechanism may be allergic, by flooding the circulation with unusable iron.

Case 2 is interesting in that this patient was a lifelong asthmatic. It will be recalled that, in the main, her reaction to intravenous iron in toxic doses was bronchospasm as characterized by wheezy dyspnoea. The factor of allergy in asthma is not disputed, neither is the ultimate cause of the symptoms—histamine release. However, the question whether the reactions in this case were due to iron or "asthma" is difficult to answer. Some evidence in favour of iron may be gathered from Ramsey (1950), who described a patient with tightness of the chest five hours after receiving 600 mg. Sinclair and Duthie (1949) also mentioned a case with bronchospasm occurring a few minutes after a dose of 200 mg. The question of dosage is relevant, in that in most recorded cases the provocative dose was 200 mg. or over. In Case 2, however, as little as 5 mg., or at other times 60 mg. and 100 mg., was necessary. It is well known that allergic subjects differ in their response at different times both to the specific allergen and to non-specific factors: for example, in hay-fever, exposure to pollen may or may not produce an intense attack of sneezing, as may rubbing the nose or injuring it in some way. Again, allergic symptoms are usually referable to the tissue most sensitive to the appropriate stimulus: for example, skin-allergy—itching, flushing, etc.; and bronchial allergy—wheezy dyspnoea, nose-sneezing, etc.

The essential cause of allergy and anaphylaxis is release of histamine, large amounts of which are present in lung and skin. This distribution may account for the flushing and bronchospasm seen in these cases. Histamine is, of course, normally found in the tissues, and immunization against it occurs from the formation of protein–histamine compounds. Its release is facilitated by trypsin and by injecting toxins, such as bee venom, staphylococcus, *Clostridium welchii*, etc. Most of the blood histamine is in the blood cells, and iron may well act as a release factor by allowing leakage to occur in some way from the blood cells into the plasma. The usual release method is by haemolysis. Case 2 was treated by sterazol (a sulphone compound), but the only evidence that could be ascribed to haemolysis was the persistently low haemoglobin level, despite continued iron therapy, followed by a fairly rapid rise to 81% on cessation of the drug.

Foster Kennedy (1951) stresses the importance of allergy in diseases of the central nervous system and believes that many phenomena—for example, migraine, epilepsy, encephalopathy—are due to local intracranial oedema, the result of allergy. Iron encephalopathy and headache could well be due to this cause. He thinks that inherited chemical patterns may determine the onset of allergy in any patient. This may well account for the tissue localization as well. Bearing on this is the opinion of Spencer (1951). From a study of ferrous sulphate poisoning in children he concluded that iron intoxication results in a widespread interference with cell function, especially in the brain, and that such central nervous system damage accounts for the symptomatology. This widespread interference could well be due to allergy—a widespread cellular upset with special emphasis on sensitized tissues.

The toxic effects of intravenous trivalent arsenicals such as neoarsphenamine bear some resemblance to those of intravenous iron. During or immediately after their injection vasomotor symptoms (also known as anaphylactoid and minor nitritoid symptoms), urticaria, and syncope occur. Following the injection, usually a few hours later, rigors, pyrexia, headache, pain in the back and limbs, vomiting, and diarrhoea also occur. Harrison (1942) thinks that these symptoms simulate anaphylaxis, and that all these compounds tend to damage capillary endothelium, with resultant petechiae in various organs, especially lung, liver, kidney, and brain. Tate (1948) also considers that arsenical dermatitis is an allergic phenomenon due to the interaction of an arsenic compound with epidermally fixed antibodies, although he acknowledges that Peters's experiments are more important. Peters (1950) has shown in classical experiments that the toxicity of arsenic depends on interference with the oxidizing enzyme pyruvate oxidase, which assists in the breakdown of glycogen to pyruvate. Dimercaprol forms a more stable ring compound with arsenic, thus regenerating the original enzyme. It has been shown that iron is intimately concerned in oxygen transport, but whether its toxicity is due to some similar act of competitive interference remains to be proved.

The nature of injected iron itself has been commented upon by many workers (Goetsch *et al.*, 1946; Ramsey, 1950; Klopper, 1951; Birch and Till, 1951). Goetsch *et al.* (1946) think that the effects may be due to a "heavy metal"

effect. Heavy metals produce pharmacological effects only when dissociated into ions of the metal or an oxide of the metal (E. M. Graham, 1951, personal communication). Spencer (1951) thinks that the free iron may combine with SH groupings and thereby interfere with oxidation. Klopper (1951), however, does not agree that toxic reactions are due to free iron. He compares the behaviour of iron to that of copper. If the latter is bound to the same protein molecule (which Klopper thinks is very likely), toxic reactions may be due to the appearance of copper selectively displaced from its protein substrate by its saturation with iron. Again, if the sulphydryl effect is the mode of action of iron-poisoning, then dimercaprol should be an effective antidote. Somers (1947), however, has shown that, in mice at any rate, dimercaprol increases the toxic effects of iron, whether used orally or intravenously.

Flocculation of the iron itself has been mentioned by Birch and Till (1951). Polson (1928) found that pulmonary embolism occurred on injection of dialysed iron. As described by Heath *et al.* (1932) and Nissim (1947), the chief reaction to intravenous colloidal ferric hydroxide is the precipitation of iron in the blood, leading to multiple emboli in the lungs and elsewhere. No such reaction has been ascribed to the widely used commercial preparations of to-day. Birch and Till (1951) stress that they used a "home-made" preparation.

The power of plasma globulin to bind iron is rapid but variable (Klopper, 1951). The question of a transient temporary concentration—for example, of *free* iron saccharate—in the plasma cannot be completely discounted. This transient effect could only account for immediate reactions, if at all, for it is unlikely that free iron would remain uncombined in the plasma after 6 to 12 hours. The occurrence of pain in the limbs and back might be accounted for by venospasm, the result of irritation by the free compound itself. Beaumont and Dodds (1952), however, think that impurities in the sugar used in the preparation may cause severe angina-like pains in the chest, arms, and back. They also think that rapid injection causes venospasm.

The question of the substrate itself acting as a toxic factor can, I feel, be discounted on the grounds that similar reactions have been described with different preparations, the only common factor being the iron itself.

Finally, Prain (1949) suggests that liver failure is the cause of death in iron poisoning, but the histological changes seem scarcely sufficient to account for this, for they are much less than in acute yellow atrophy. Death also occurs more quickly in iron poisoning than in liver atrophy. It would seem more likely that death is due to the widespread interference with cell function which undoubtedly occurs, whether this be caused by the iron itself or by anaphylaxis.

In conclusion, it must be conceded that the severity of iron reactions seems to depend on the dosage employed. The most severe reactions occurred with doses of 100 mg. or over. Wilkinson and Slack (1949) used 25 mg. of their original preparation of iron-sucrose as a starting dose, but Beaumont and Dodds (1952) use 50 mg. It would therefore be as well to employ doses of this order at the start if severe reactions are to be avoided.

Summary

The causation of iron intoxication is reviewed in the light of two further cases occurring in tuberculous patients.

From the work of Laurell, Klopper, and others it is concluded that an iron–protein complex is formed in the blood, the protein component being a globulin. Laurell's hypothesis of a saturation limit is further discussed in relation to the iron-binding capacity of the plasma proteins. This depends on several factors, including severe liver disease and severe infections.

The disturbance of protein metabolism occurring in liver disease and severe infections such as tuberculosis is suggested as being responsible in part for the occurrence of iron-reactions in these subjects.

Both patients were anaemic. Following Anderson's animal experiments, it is further suggested that anaemia may explain the rapidity of the onset of symptoms in these cases. The question of allergy is considered in relation to Landsteiner's work on drug allergy. The protein moiety of the iron–protein complex postulated above is suggested as being responsible for the allergic phenomena seen in the second case—pallor, wheeziness, and cough.

The severity of iron reactions in general would seem to depend on the dosage injected; the most severe reactions occurred after 100 mg. or more was given. The use of a small initial dose, say 25 to 50 mg., is stressed.

Graduated doses may act as desensitizing agents by presumably increasing the amount of iron-binding protein used per injection.

The essential cause of allergic symptoms—histamine release—is also considered in relation to the main toxic signs—flushing and bronchospasm. It is suggested that these occur because the largest amounts of histamine are present in the skin and lungs. The toxicity of iron is further compared with that of intravenous arsenic. An alternative hypothesis is put forward that iron acts, like arsenic, by competitive interference with an enzyme system. A sulphydryl effect is discounted on the grounds that dimercaprol *increases* the toxic effects of iron.

Finally, the cause of death is reviewed: the suggestion is put forward that death results from widespread interference with cell-function, probably due to an anaphylactic mechanism.

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AURICULAR PAROXYSMAL TACHYCARDIA IN CHILDHOOD

BY

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In the adult, auricular paroxysmal tachycardia is characterized by a sudden onset and offset, a rapid heart rate (usually 160 to 180 beats a minute), and, more often than not, a regular rhythm. The disturbance is usually transient. It is the most common and least important type of paroxysmal arrhythmia, and is usually associated with an otherwise normal cardiac mechanism. The diagnosis is made with certainty by electrocardiogram. Calisthenic movements, of arm-stretching or body-bending, and vagal stimulation by pressure on the eyeball or carotid sinus are recommended as useful first measures and are often successful. Should such manœuvres fail, the drug of choice is methacholine.

In reviewing the literature, and in recording personal observations in cases of auricular paroxysmal tachycardia, it is hoped to make quite clear in how many respects the condition and its treatment differ in childhood from those in the adult.

Hubbard (1941) reviewed the literature in regard to the condition affecting infants. He found details of only 19 cases, and added nine from his own experience. Of these nine, he observed six in the same year, and could not help assuming that the condition was not as rare as the literature suggested.

The clinical records of a further 38 cases reported in the literature have been studied and summarized. In all but the first of these cases the diagnosis was confirmed and the heart rate counted by electrocardiogram. Six cases personally observed in the years 1948–51 have been added, in five of which the electrocardiogram tracing was interpreted as that of supraventricular tachycardia. No tracing was obtained in the first case.

Case 1

A male child aged 4 weeks refused feeds for one week and had laboured breathing for two days. The diagnosis before admission to hospital was pneumonia. Presenting signs were laboured breathing; cyanosis; liver enlarged two fingers below right costal margin; oedema present over feet, ankles, and sacrum; heart rate of approximately 300 a minute; and fine crepitations limited to the lung bases. No electrocardiogram or *x*-ray film of the chest was obtained before treatment.

Progress and Treatment.—Neostigmine, 0.125 mg., was given intramuscularly, and within 20 minutes the heart rate slowed to 120. Clinical improvement ensued, and within 24 hours the infant was normal in all respects. Digoxin, 0.025 mg. daily, by mouth was given for four days and then discontinued. The infant remained well. There was no clinical evidence of congenital heart disease.

Follow-up.—The patient, when last seen two months after the initial illness, was clinically well, and the heart was noted to be normal in size, sounds, and rate.

Case 2

The mother of a male child aged 19 weeks noticed the infant's heart thumping when bathing or dressing him. Presenting signs were mild cyanosis; minimal oedema over feet, ankles, and sacrum; liver enlarged two fingers below right costal margin; heart enlarged; heart rate 280; and raised venous jugular pressure. *X*-ray examination of the chest showed generalized enlargement of the heart and clear lung fields. The electrocardiogram revealed supraventricular tachycardia with 2–1 A.V. response. In Fig. 1 the second P waves can be seen on top of the R waves in the lead CR1. In view of the A.V. block some cardiologists would interpret the tracing as auricular flutter.

Progress and Treatment.—Pressure was applied to the eyeballs and carotid sinus without benefit. Three intramuscular injections of neostigmine of 0.125, 0.125, and 0.25 mg. at half-hourly intervals were then given without effect on heart rate or clinical picture. Following this, tincture of digitalis, 5 minims (0.3 ml.) twice daily was given for eight days, when the heart rate slowed to 115, with clinical improvement. A maintenance dose of 2½ minims (0.15 ml.) of tincture of digitalis was continued for some three months.

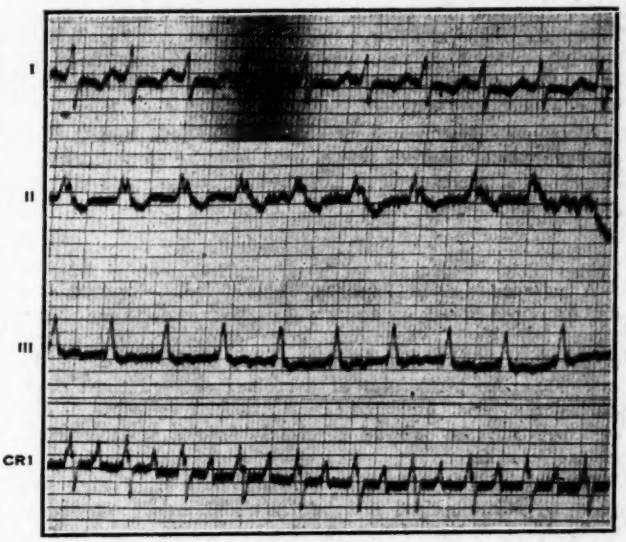

FIG. 1.—Electrocardiogram of Case 2.

Follow-up.—The patient's condition was reviewed at intervals for 18 months after withdrawal of the digitalis. He remained clinically well and the heart was noted to be normal in size, sounds, and rate.

Case 3

A female child aged 3 months failed to gain weight and vomited. Presenting signs were enlarged heart with systolic murmur; enlarged liver, four fingers below right costal margin; oedema over feet, ankles, and sacrum; raised venous jugular pressure; and heart rate of 240. No signs

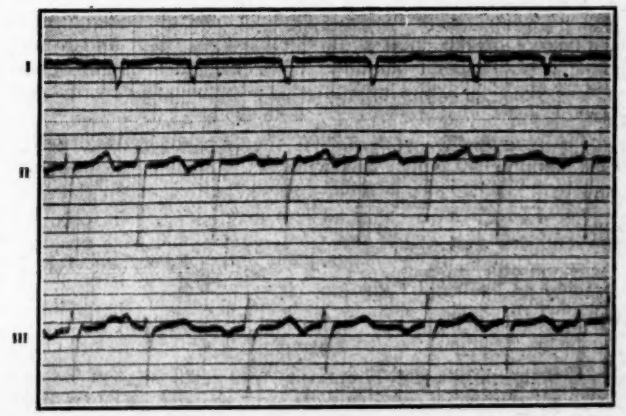

FIG. 2.—Electrocardiogram of Case 3.

suggesting pneumonia were detected in the chest. An *x*-ray film of the chest showed consolidation in the right upper zone and an enlarged heart shadow.

The electrocardiogram was very difficult to interpret. Supraventricular tachycardia was present. Lead II was regular except for one beat, and inverted P waves appear to precede each QRS complex, which is of normal type (Fig. 2). No definite evidence of conduction defect. In Lead III the rhythm is irregular, and, although most of the P waves are inverted, one upright P wave is clearly seen. Presumably this is due to a shifting pace-maker.

Progress and Treatment.—As well as penicillin, digoxin by mouth, 0.125 mg. three times daily, was given. Within four days the heart rate was slowed to 150 and the signs of cardiac failure were reduced. The child died seven days after beginning treatment.

Necropsy.—Pneumonia was present in both lungs. The interventricular septum was patent and the foramen ovale open. No microscopical examination was made of the cardiac conducting system.

Case 4

A male child aged 2 months refused feeds, vomited, and had laboured breathing and a poor colour. Presenting signs were right basal pneumonia, liver enlarged three fingers below the right costal margin, heart enlarged, and heart rate 300. An *x*-ray film of the chest showed right basal pneumonia and enlarged cardiovascular shadow. The electrocardiogram showed absolutely regular supraventricular tachycardia.

Progress and Treatment.—Neostigmine, 0.125 mg., was given by intramuscular injection at half-hourly intervals for three doses without effect on the heart rate. Tincture of digitalis, 1 minim (0.06 ml.) four times daily, was then given for eight days, when the heart rate slowed to 140. Three days later the heart rate returned to the region of 300. Digoxin, 0.125 mg. by mouth three times daily, was recommenced and continued for one week, resulting in reduction of the heart rate to 150. After a further 12 days without treatment the infant became ill again with the heart rate and clinical picture as at the onset of his illness. Digoxin was readministered with good result, and the child was sent home, having a maintenance dose of 0.125 mg. daily. He had no further cardiac disturbance, but six months after his initial illness he died of rapidly increasing hydrocephalus.

Necropsy.—Hydrocephalus was associated with scarring and thickening of the meninges, presumably due to an old inflammatory lesion and causing a blockage at the lower surface of the cerebellum. No macroscopic abnormalities were detected in the heart.

Case 5

A female child aged 2 years had a cough for two months after whooping-cough. On admission breath sounds were normal, and the heart rate 250. There was mild cyanosis, but no enlargement of heart or liver and no oedema. An *x*-ray film of the chest showed clear lung fields and a normal cardiovascular shadow. The electrocardiogram was interpreted as showing auricular tachycardia with 1–1 response.

Progress and Treatment.—As the signs of cardiac defeat were minimal digitalis was withheld. The heart rate spontaneously slowed to normal over a period of 10 days.

Follow-up.—Two years after discharge from hospital the patient was well and the heart was normal in size on *x*-ray examination, with a rate of 82 a minute in the E.C.G. tracing and normal heart sounds.

Case 6

A male child aged 17 months was restless, slept poorly, had poor appetite, and had general malaise for two days. Presenting signs were restlessness, a mild degree of cyanosis, liver enlarged two fingers below right costal margin, heart slightly enlarged, and heart rate approximately 300; no heart murmur was detected. An *x*-ray film of the chest showed generalized enlargement of the heart and heavy vascular markings in the lung fields. The electrocardiogram showed supraventricular tachycardia, rate 315, rhythm regular.

Progress and Treatment.—Digoxin, 0.125 mg., by mouth, was given six-hourly. After 10 doses the heart rate suddenly slowed to within normal limits, with clinical improvement. The child went home, having a maintenance dose of digoxin, 0.125 mg. by mouth, on alternate days.

Follow-up.—Six months after discharge from hospital digoxin was discontinued, and after a further six months the patient was noted to be clinically well. The heart was normal in size on *x*-ray examination, with a rate of 84 a minute in the E.C.G. tracing and normal heart sounds.

Discussion

Cases in the Literature

In this survey the details from a total of 66 cases are used. These cases consist of the 19 reviewed by Hubbard (1941), the 9 personally observed by him, and 38 recorded in the literature since 1941. I do not claim that the whole of the literature on the subject is reviewed.

The commonest recorded symptoms were vomiting in 16 and laboured breathing in 14 cases. The commonest signs observed were enlarged liver in 28, cyanosis in 15, pallor in 11, and oedema in only 2 cases. The lowest heart rate recorded was 210, and the fastest without heart block 365. The duration of attacks varied between a few minutes and five months. Of associated diseases the most common were diphtheria and pneumonia. As a therapeutic measure digitalis was the most popular, being employed in some form in 19 of 40 cases. Of these 19 children, 14 recovered. Fourteen children received no specific therapy directed towards controlling the heart rate, and of these only four recovered.

Campbell (1947), when reviewing the subject in all age groups, advised that in cases without serious heart damage the order of choice in regard to drugs used in treatment is methacholine, neostigmine, carbachol, and quinidine. Methacholine alone was effective in two cases. The drug is usually given hypodermically, but has been given intravenously. The usual dose in children is 0.2–1 mg., but 6 mg. has been given in one dose. Atropine sulphate, 1/150–1/100 gr. (0.4–0.65 g.), is the antidote, and a syringe loaded with this preparation should always be in readiness when methacholine is to be used, as its administration in children is not without danger. Neostigmine was mentioned in the treatment of only one case. This drug may be given intramuscularly or intravenously, usually the former. The dose in children is 0.2–1 mg. Quinidine alone was effective in one case. In children the dose is of the order of ¼ gr. (16 mg.) 12-hourly, with a maintenance dose of ¼ gr. (16 mg.) daily. With this drug there is always the possibility of idiosyncrasy, a risk which is considerable when dealing with an infant already usually gravely ill.

Cunningham and Schnitzker (1950) used phenylephrine with dramatic effect. There were short periods of cardiac arrest after its use. They gave the drug intravenously, and recommended 0.1 mg. at half-hourly intervals, increasing up to as large a dose as 0.5 mg.

Present Series

In these six cases the commonest symptoms were vomiting in three and laboured breathing in four. The commonest signs observed were enlarged liver in five, cyanosis in five, oedema in five, and pallor in three cases. The range of heart rate was between 240 and 315. In Cases 2 and 4 the rapid heart rate persisted until the eighth day

of treatment and then suddenly the rate was reduced. Pneumonia as an associated disease was present in Cases 3 and 4.

Only two drugs were used to reduce the heart rate—neostigmine and digitalis, the latter as tincture or digoxin. Neostigmine was effective in Case 1. The dose given was 0.125 mg. by intramuscular injection to an infant of 4 weeks. In the other five cases digoxin or tincture of digitalis by mouth was effective. Digoxin orally seemed to be the drug of choice. A suitable dose was 0.125 mg. repeated two or three times daily until the heart slowed. Even the smallest babies tolerated such a dose, and indeed it seemed necessary to control the rapid heart action.

Summary

Auricular paroxysmal tachycardia is less rare than is often supposed.

In the cases seen in hospital the so-called " paroxysm " usually lasted several days.

The common clinical picture in childhood is that of cardiac failure associated with an extremely rapid heart rate (200–350 beats a minute). The insidious onset of such failure is frequently missed in children unless looked for.

Pneumonia may be the assumed diagnosis, and indeed is often present in addition to the tachycardia. Both conditions demand treatment.

The incidence of congenital heart disease in association with auricular paroxysmal tachycardia seems to be quite low.

Digitalis would appear to be the drug of choice in treatment. Large doses are tolerated in infancy and seem necessary for recovery. A smaller maintenance dose for four to eight weeks should be given to prevent early recurrence of the tachycardia.

I wish to thank Dr. T. Colver and Professors R. S. Illingworth and E. J. Wayne, under whose care some of the cases were admitted to hospital; Dr. J. F. Goodwin for his advice, and especially for his interpretation of the E.C.G. tracings; and Dr. B. R. Eaton for his help in obtaining the tracings.

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The film " Streptomycin Drugs in the Treatment of Tuberculosis " has been withdrawn from the B.M.A. Film Library by Messrs. E. A. Squibb and Sons, from whom it was held on loan, because the methods of treatment and dosages depicted therein are now out of date.

EFFECT OF HYDRALAZINE IN HYPERTENSION

BY

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Hydralazine (1-hydrazinophthalazine; " apresoline ") has recently been under investigation both in the laboratory and clinically as an antihypertensive drug. Pharmacologically, its exact action is not known. It is an antihistaminase and has a wide range of activity in antagonizing humoral pressor substances—that is, hypertensin, pherentasin (Schroeder, 1952), serotonin (Taylor *et al.* (1951), and *nor*adrenaline (Freis and Finnerty, 1950). There is suggestive evidence of a central action on the hypothalamus (Gross *et al.*, 1950; Craver and Yonkman, 1950) and on peripheral arterioles. It has been shown that, associated with a decrease in peripheral resistance—preferentially marked in the kidneys—and a decrease in blood pressure, there is a pronounced tachycardia and an increase in cardiac output due either to a central effect or to local action of the drug on the heart (Moyer *et al.*, 1951). There is an increase in the renal blood flow without constant increase in the glomerular filtration rate (Mackinnon, 1952) or any increase in tubular resorption of glucose, indicating that no additional nephrons are activated by the increase in renal blood flow (Moyer *et al.*, 1951). No previously known antihypertensive drug has been shown to have this combined effect of decreasing the blood pressure and increasing the renal blood flow.

The Investigation

Selection of Cases and Method of Recording.—In the present study the effect of hydralazine was observed on arterial hypertension in 12 cases—nine suffering from essential hypertension, one from hypertension complicating chronic pyelonephritis, and two from malignant hypertension. All had hypertensive symptoms. In two cases of essential hypertension (Cases 3 and 6) blood pressures showed wide fluctuations, often related to psychological disturbances. Auscultatory blood-pressure readings were taken frequently in upright, sitting, and recumbent positions during a control period of 3 to 13 days, and, after the drug was given, pressures were taken in the same positions at intervals for six hours; averages of control readings, and these readings after the drug, are given in the Table overleaf.

Dosage.—Hydralazine was administered orally in all trials. A test dose of 25 mg. was first given, and the dose was gradually stepped up from 25 mg. eight-hourly to higher levels reaching 400 mg. three times a day, thus varying from 75 to 1,200 mg. a day in different patients. Every attempt was made to continue treatment unless it was considered futile or the side-effects were so unpleasant and persistent as to warrant discontinuation of the drug. The effect of the drug lasted from four to six hours, with a maximum at from one to two hours after administration. In addition to oral treatment, parenteral therapy with hydralazine in doses of 50 mg. intramuscularly was tried in two cases, only one of which is tabulated (Case 5). The effect of combined oral therapy with hexamethonium bromide and hydralazine, as suggested by Schroeder (1952), was studied in Cases 4, 7, 8, and 9. The maximum daily doses tried were 2,250 mg. of hexamethonium bromide and 450 mg. of hydralazine.

Oral Therapy with Hydralazine

Case No.	Age and Sex	A. Type of Hypertension and B. Clinical Condition	Control Period (days)	Average Control B.P.			In-patient Treatment (days)	Largest Dose (mg./day)	Average B.P. During Treatment			Severity of Side-effects	Remarks
				Standing	Sitting	Recumbent			Standing	Sitting	Recumbent		
1	42 M	A. Essential hypertension B. Angina pectoris. Heart +. E.C.G., L.V. ++. Fundi: A/V nipping +. Renal function: fair	4	188/128	188/129	183/126	33	900 orally	179/119	178/120	176/116	Mod. severe	Treatment abandoned because of: (1) no appreciable effect on hypertension; (2) side-effects
2	32 M	A. Essential hypertension B. Congestive cardiac failure (early). Hypertensive encephalopathy. Heart +. E.C.G., L.V. +++. Fundi: haemorrhages and exudates. No papilloedema. Left optic atrophy (old central retinal artery thrombosis). Renal function: fair	3	200/125	200/122	202/120	18	1,200 orally	199/117	200/117	196/113	Slight	Treatment abandoned because of no appreciable effect on hypertension
3	60 M	A. Essential hypertension B. Angina pectoris. Heart +. E.C.G., L.V. ++. Fundi: nothing abnormal detected. Renal function: good	13	210/109	216/112	213/110	30	600 orally	189/94	187/98	186/97	Slight	Control B.P. showed much fluctuation, which continued at lower levels during treatment period. Later out-patient observation showed that the slight B.P. reduction of first month was not maintained
									Average B.P. in last week of out-patient follow-up while on treatment				
									201/112	208/113	212/115		
4	62 F	A. Hypertension complicating chronic pyelonephritis. B. Heart +. E.C.G., L.V. +. Fundi: exudates in left fundus. No papilloedema. Renal function: advanced renal failure	4	215/125	220/122	215/122	11	300 orally	189/110	192/112	184/103	Mod. severe	Treatment abandoned because of (1) side-effects—patient refused to continue treatment with the drug; (2) inadequate response
									Combined therapy with hexamethonium bromide and hydralazine				Effect of combined therapy with oral hexamethonium bromide and hydralazine studied on readmission of patient. The favourable response in hospital not maintained in the out-patient follow-up
							20	Hex. brom. 750 Hydral. 300	169/101	170/102	170/100	Mod. severe	
									Average B.P. in last week of one month's out-patient treatment				
									208/123	207/123	197/120		
5	53 M	A. Essential hypertension B. Angina pectoris. Heart +. E.C.G., L.V. ++. Fundi: A/V nipping +. Renal function: fair	4	200/120	210/125	210/120	2	50 mg. I.M. inj. daily	142/89	156/95	168/99	Severe	Parenteral therapy had appreciable effect on B.P. but had to be abandoned because of side-effects. Oral therapy then resorted to
							6	450 orally	173/105	183/107	190/109	Mod. severe	Treatment abandoned because of (1) side-effects; (2) inadequate response
6	39 F	A. Essential hypertension B. Heart: L.V. +. E.C.G. within normal limits. Fundi: nothing abnormal detected. Renal function: good	5	164/109	164/109	164/106	10	300 orally	153/96	155/96	151/95	Mod. severe	B.P. in control and treatment period showed fluctuations because of large psychological overlay. Treatment abandoned because of side-effects and inadequate response
7	50 F	A. Essential hypertension B. Heart +. E.C.G., L.V. +. Fundi: A/V nipping. Renal function: good	4	212/122	214/122	210/120	23	Hex. brom. 1,500 Hydral. 450	164/98	170/98	167/100	Mod. severe	Considerable reduction of B.P. shown by patient while in hospital not maintained in out-patient follow-up
									Average B.P. after two weeks out-patient treatment				
									225/135	227/132	222/130		
8	59 F	A. Essential hypertension B. E.C.G., L.V. strain or ischaemia. Fundi: N.A.D. Renal function: good	5	224/137	216/137	217/135	8	Hex. brom. 2,250 Hydral. 450	205/127	200/128	200/128	Mod. severe	No appreciable reduction of B.P. achieved
9	51 M	A. Essential hypertension B. Heart +. E.C.G., L.V. ++. Fundi: haemorrhages and exudates. No papilloedema. Renal function: good	5	233/142	226/135	232/138	14	Hex. brom. 2,250 Hydral. 450	208/132	206/128	206/127	Slight	No appreciable reduction of B.P. achieved

Side-effects.—In all patients the side-effects were similar in nature but not in severity, and were much more pronounced after parenteral administration. Cases 2, 3, 8, and 9 got over these reactions after about a week's treatment, but others could not get used to the drug at all. The side-effects noted were: (1) headaches, heaviness, and throbbing in the head; (2) flushing and sweating of the face—a sense of heat in the face and head; (3) dryness of the mouth, nausea, vomiting, anorexia, and epigastric discomfort; (4) a feeling of chill and shivering; (5) yawning and sleepiness; (6) tachycardia; (7) slight hyperpnoea; (8) transient erythematous rash; (9) lethargy, tiredness, and loss of interest in everyday affairs; and (10) giddiness on standing, especially after parenteral therapy.

Results

Parenteral Therapy.—Despite its pronounced hypotensive effect in the early stages, this method had to be abandoned because of unpleasant side-effects (Case 5).

Oral Therapy.—In Cases 1, 3, 4, 5, and 6 this caused some lowering of pressures in the first few days of the trial, but hypertension quickly became resistant even to the higher doses of the drug, and the sum total of results was not encouraging. In Case 2 the treatment had no effect at all on the hypertension. In one case (not mentioned in the Table) the patient had such unpleasant side-effects from the test dose of 25 mg. that she refused to take further doses of hydralazine, and preferred injections of hexamethonium bromide: the test dose was without effect on the blood pressure. In two cases of malignant hypertension oral therapy was tried between effective injections of hexamethonium. No further action was noted on the blood pressure: the results are not tabulated.

Combined Oral Therapy (Hexamethonium Bromide and Hydralazine).—This method was tried in Cases 4, 7, 8, and 9. There was some lowering of the pressures in the first few days of the trial, but the hypertension quickly became resistant even to higher doses of the drugs.

Discussion

Various claims of beneficial results from oral hydralazine are not substantiated by the experience recorded above. Page (1951) has stated that good responses to oral doses may not be achieved until patients have been on the drug for 10 days or more. This claim is not supported by our results, but rather the reverse—that is, apparently good results at the beginning are not maintained after a week or two. When patients are receiving hexamethonium it has often been noted that vasodilatory influences such as meals, hot weather, or intercurrent fever may enhance the blood-pressure-reducing action of the drug. However, the addition of hydralazine to hexamethonium therapy did not seem to make the latter treatment any more effective.

Summary

The effect of hydralazine alone and in combination with oral hexamethonium bromide was studied in 12 patients suffering from hypertension. In most of these there was a slight reduction of blood pressure at the beginning of treatment, but this was not maintained later in spite of a great increase in dosage. Persistence of unpleasant side-effects was noted in most of the patients.

I am grateful to Professor J. McMichael for his constant help and guidance in the preparation of this paper. I am also indebted to Ciba Laboratories Ltd. for trial supplies of apresoline.

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EFFECT OF P.A.S. ON THE THYROID GLAND

BY

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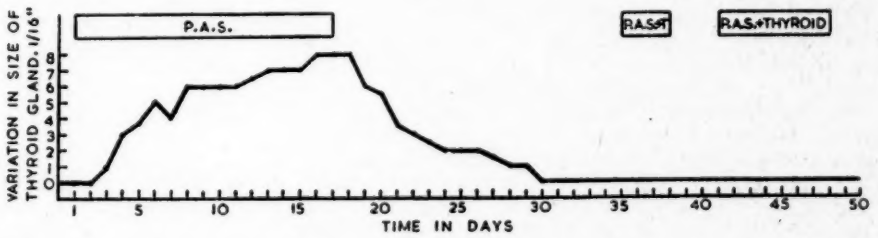
Enlargement of the thyroid gland after the administration of P.A.S. has been reported on several occasions (Bergquist and Mare, 1951; Clausen and Kjerulf-Jensen. 1951; Komrower, 1951). In the following case observations showed that the P.A.S. was the direct cause of the enlargement and that the administration of thyroid extract along with the P.A.S. prevented it. An unusual feature was the development of exophthalmos.

Method Used to Estimate Variation in Size of the Thyroid Gland.—A plaster-of-Paris cast was made of the patient's chin and sternal notch, a pencil being placed between the two and incorporated in the plaster. When this was held in position by the patient the neck was fixed at a constant angle. Three fixed points were next placed on the patient's neck overlying the thyroid gland, and the distance between them was measured daily. It was thought that any variation in the measurement reflected an increase or decrease in the size of the thyroid. By this method it was possible to detect a variation of 1/16 in. (1.5 mm.).



Case Report

The patient, a young man aged 19, suffered from bilateral pulmonary tuberculosis with extensive cavitation of both lungs. On two occasions prior to the present observations the patient had developed an enlargement of the thyroid while receiving P.A.S.; this rapidly subsided when the drug was stopped.

In December, 1951, the administration of P.A.S. was again started, 7.5 g. being given daily in divided doses; the effect on the thyroid gland is shown in the accompanying Graph.

Enlargement of the gland was first noted on the third day; it continued until the seventeenth day (total dosage, 123.5 g.), administration being stopped because of toxic symptoms consisting of loss of appetite, vomiting, headache, dizziness, and slight exophthalmos. On stopping the drug the thyroid began to decrease, and by the twenty-ninth day had returned to its original size. It would seem that the P.A.S. was the direct cause of the enlargement, and that the enlargement was proportional to the total dosage given.

On the thirty-fifth day the patient was again given P.A.S., 7.5 g. a day, plus thyroid *B.P.*, 1 gr. (65 mg.) thrice daily. Three days later both drugs were stopped on account of toxic symptoms. After a rest of three days the drugs were again administered, this time being continued for seven days, when again the drugs were stopped on account of toxic symptoms. No enlargement of the thyroid was noted during this period, and it seems that the addition of the thyroid extract prevented the gland from enlarging. The toxic symptoms noted were again loss of appetite, vomiting, headache, and dizziness, with persistence of the exophthalmos; the patient stated that the addition of thyroid extract increased these symptoms. Observations on the temperature and pulse rate were not instructive, although the lowest pulse recorded (76) occurred when the size of the gland was maximal.

Discussion

The literature offers no explanation of the effect of P.A.S. on the thyroid gland. Observations on this patient reveal certain interesting facts; first, that the P.A.S. was the cause of the enlargement; and, secondly, that the enlargement was probably controlled by thyroid extract. If these two observations are correct, one must assume that the enlargement was hyperplastic and hypothyroid in type. This view would agree with the findings of Komrower (1951), who reports a case of myxoedema associated with thyroid enlargement. In fact, so far as is known, all cases reported have been hypothyroid in type. It is further noted that the effect on the thyroid gland in certain experimental animals is to reduce the amount of colloid present. It is therefore suggested that P.A.S. produces its effect on the thyroid gland in the same way as thiouracil—by interfering with the production of the thyroid hormone.

Attention is drawn to an unusual effect of P.A.S. *in vitro* Horn and Bogsch (1950) report that P.A.S. binds a large amount of iodine from a solution. One molecule of P.A.S. binds three atoms of iodine, and it is possible that P.A.S. interferes with the production of thyroxine by binding iodine and preventing the iodization of tyrosine.

If P.A.S. has a thiouracil-like action this might explain in part some of the clinical findings following its administration—in particular, the gain of weight, slowing of the pulse, and lowering of the temperature. As the tuberculosis physician says, "It makes a hot tubercle cold."

Summary

A case of thyroid enlargement with exophthalmos is reported following treatment by P.A.S.

It is suggested that P.A.S. produces its effect by binding iodine and so preventing the iodization of tyrosine. It may thus have a goitrogenic effect similar to that of thiouracil.

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A serious outbreak of rabies in Alberta, Canada, is spreading to neighbouring areas of Saskatchewan and Manitoba, according to recent reports in *The Times*. The rabies was first detected last June among wild animals, particularly wolves and foxes, in northern Alberta, but the danger is that the disease may affect domesticated animals or even man. Rabid wolves lose their fear of man, and they may attack cattle, pigs, or dogs, all of which are susceptible to the disease. If rabies becomes established among the sledge dogs the fur trappers who earn their livelihood in the north will be very seriously threatened. The dogs are indispensable to them. Vigorous steps have been taken to limit the epidemic. The Government of Alberta has embarked on a wide-scale campaign to poison wolves and foxes; all dogs in Alberta, Saskatchewan, and Manitoba north of 55° N. have been quarantined; and sledge dogs are being vaccinated.

Medical Memorandum

Sublingual Mumps

Although precise figures of the incidence of mumps involving only the sublingual glands are not given in many of the textbooks, this condition must be uncommon enough to lead on occasion to confusion, if not error, in diagnosis. Banks (1952, personal communication) could remember seeing only one case, and quoted a series of 77 cases in which, although the percentage of non-parotid types was unusually high, only one sublingual case occurred, an incidence of 1.3%. In his opinion the pure (or almost pure) sublingual type is about as rare as the case involving the lacrimal glands described by Galpine and Walkowski (1952).

Because of its serious complications, the importance of recognizing the infection is obvious. In a series of 14 cases of mumps meningo-encephalitis reported from the Bristol area by Macrae and Campbell (1949) six occurred before other signs of mumps developed. No pure sublingual case was noted in the series of 208 cases described by Laurence and McGavin (1948); 13 were submandibular (submaxillary) types, and orchitis was the only manifestation of the infection in five cases. According to Banks (1949), "Sublingual gland enlargement is not common, but it may be the only sign of the disease, in which case the diagnosis is easily missed."

CASE REPORT

On August 11, 1952, a boy aged 11 complained of a sore throat and pain on swallowing. On examination his temperature was 99.8° F. (37.7° C.), pulse rate 100. (He had been given 5 gr. (0.32 g.) of aspirin the previous evening.) There was a large swelling under the mandible, the overlying skin being pale, shiny, and tense. The soft tissues forming the chin were displaced forward by the swelling, giving the face a peculiarly pugnacious appearance. Bimanual palpation showed that the sublingual glands were very swollen and tender; no swelling of the submandibular (submaxillary) or parotid glands could be detected at any time. The tongue appeared swollen and discoloured; its mobility was restricted, with consequent thickness of speech; and halitosis was pronounced. Under the tongue there was a remarkable degree of oedema of the terminations of Wharton's and the sublingual ducts, and the adjacent mucosa; the palate, fauces, pharynx, and the orifice of Stensen's duct appeared normal. Sialorrhoea was continuous and profuse.

On August 12 (the fourth day of symptoms) it was thought that the local signs had reached a maximum. The next day a blood examination showed total white cells 9,900 per c.mm. (polymorphs 62%, lymphocytes 24%, monocytes 8%, eosinophils 6%). These counts were within normal limits, although a relative lymphocytosis is described as occurring commonly. The serum amylase activity was 55 units per 100 ml., which was to be expected in a "non-parotid" case (Wolman *et al.*, 1947).

On August 14 the temperature had dropped to 98.4° F. (36.9° C.) and the child felt much brighter, although five more days elapsed before the sublingual oedema had subsided and the mouth could be opened fully without discomfort. A fortnight elapsed from the beginning of symptoms before the swelling and tenderness of the sublingual glands disappeared. No symptoms suggestive of cerebral, abdominal, genital, or other complications occurred, with the exception of bradycardia (50) from the fourth to the tenth day (the child's normal pulse rate was known to be 90); no accompanying apical systolic murmur was detected.

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Reviews

DISEASES OF THE CHEST

Diseases of the Chest. Edited by Sir Geoffrey Marshall, K.C.V.O., C.B.E., M.D., F.R.C.P., and Kenneth M. A. Perry, M.A., M.D., F.R.C.P. In two volumes. Vol. I, pp. 456; 158 figures. Vol. II, pp. 413; 192 figures. (£7 7s.) London: Butterworth and Co. (Publishers) Ltd. 1952.

The editors are to be congratulated on their skill in marshalling a batch of 31 contributors, and in having achieved their object of making the volumes "reasonably comprehensive." No book on diseases of the chest would be complete nowadays without an article on the anatomy of the bronchi by Dr. Foster-Carter, and another on pulmonary tuberculosis in childhood by Dr. Margaret Macpherson. The readers will be glad to meet these two old friends in the first volume. In this volume also there is an informative article on the applied physiology of respiration. The limitations of bronchospirometry are pointed out, for, as the authors remark, the "information given from bronchospirometry is not often clinically helpful." Pulmonary tuberculosis is treated very fully from both the medical and surgical aspects. The different types of operation at present in fashion are described, but an article by a physician on the end results of surgical treatment would prove a valuable and illuminating addition. In the chapter on whooping-cough the reader is advised to give a child up to 10 years of age 20 g. of chloramphenicol spread over 10 days. This is a potentially fatal dose. On the same page the dose of ephedrine recommended is 8½ gr. three times a day for children up to the age of 5 years. This is almost certainly a fatal dose.

In the second volume we find chapters on, among other subjects, diseases of the pleura, periarteritis nodosa, asthma, emphysema, and bronchiectasis; finally, there is an account of the value of physiotherapy in diseases of the chest. The most readable and living article from the clinical point of view is, in my opinion, that contributed by Dr. Boland on asthma. Those who like *x*-ray reproductions of diseases of the lungs will be pleased to find that 200 of the 870 pages in the two volumes are given up to these illustrations. Most of them are extremely well produced, and this book forms a valuable addition to the literature of diseases of the chest.

On reading the various chapters one cannot fail to be impressed by the emphasis laid on the scientific and academic aspects of the work, and therein lies its strength. The clinical sections, however, are not so vivid. It is to be regretted that the senior editor has contributed no article to the book. With his wealth of clinical knowledge and vast experience of chest diseases he could have so enlivened the text that the reader would have arisen from its perusal stimulated and refreshed.

G. E. BEAUMONT.

YOUNG DELINQUENTS

The Young Delinquent in His Social Setting: A Glasgow Study. By Professor T. Ferguson. (Pp. 158. 10s. 6d.) London: Geoffrey Cumberlege (Oxford University Press). 1952.

In *The Young Wage-Earner*, which appeared in 1951, Professor Ferguson described an inquiry into the after histories of 1,349 Glasgow boys who left school at the age of 14. The present study forms a supplement to that broader survey. Its purpose is to investigate the incidence of delinquency within the group and to discover its apparent causes.

He finds that as many as 165 of the youths—12% of the total—had been convicted before they reached the age of 18. His chief conclusion is that a "low level of scholastic ability was probably the most powerful single factor" and that "the risk of delinquency is seriously enhanced when adverse social factors are also found." However, no attempt was made to discover whether emotional or temperamental factors might not be still more powerful than intellectual. Of the social factors the two most important appeared to be residence in an overcrowded district and frequent change of employment. The influence of a "broken home" was not so marked as other writers have supposed: indeed, among the physically handicapped "the absence of a parent" was a much less important factor than "the presence of a bad parent."

The lack of any rigorous analysis of the raw figures obtained has elicited some criticism from statistical writers, and certainly leaves the reader in doubt about the validity of many of the inferences. Nevertheless, the data obtained are tabulated in sufficient detail to enable any investigator, familiar with the pitfalls that beset these statistical and sociological inquiries, to work over the material with more elaborate techniques if he wishes. So far as they go, Professor Ferguson's own conclusions are in the main concordant with those reached in previous studies of juvenile delinquency, and, as he says, appear to demonstrate that the factors operative in Glasgow are much the same as those observed in London, Liverpool, and other large industrial areas.

CYRIL BURT.

THE SPREAD OF TUMOURS

The Spread of Tumours in the Human Body. By Professor R. A. Willis, M.D., D.Sc., F.R.C.P. Second edition. (Pp. 447; 85 figures. 63s.) London: Butterworth and Co. 1952.

When the first edition of this book appeared in 1934 it was clear that a learned student of neoplastic disease had arrived upon the scene. His later *Pathology of Tumours*, to which the present edition forms a companion volume, established Professor Willis's authority in this field. This masterly review of the ordinary and extraordinary modes of spread and metastasis exhibited by all forms, both common and rare, of tumours in the human body makes fascinating reading. The present edition follows the same pattern as the first; the text has been revised and brought up to date with the addition of 260 references. The reproduction of the photomicrographs is in general better than in the first edition. The figures are now collected at the end of the volume and their number has been reduced. All interested in neoplastic disease will gain benefit from this valuable work of reference.

DOROTHY S. RUSSELL.

HUMAN PHYSIOLOGY

The Living Body. By Charles Herbert Best, C.B.E., M.A., M.D., D.Sc.(Lond.), F.R.S., F.R.C.P.(Canada), and Norman Burke Taylor, V.D., M.D., F.R.S.(Canada), F.R.C.S.(Edin.), F.R.C.P.(Canada), M.R.C.S.(Eng.), L.R.C.P.(Lond.). Third edition. (Pp. 792; illustrated. 37s. 6d.) London: Chapman and Hall. 1952.

The third edition of this book has expanded from a popular exposition to a textbook in human physiology suitable for students for diploma courses and for medical students as an introduction to lectures and the bigger books. It now contains 400 figures as against 283 in the last edition.

The first 50 pages form a simple introduction to elementary science in so far as it is necessary to the comprehension of physiology. The introductory physics and chemistry is particularly up to date in presenting modern views on the atomic structure as an essential for the understanding of biology. The remaining 740 pages treat physiology as an organic whole, ignoring the divisions which have grown up—biochemistry, biophysics, histology—animal, mammalian, and human—and neurology. The account is well balanced from the point of view of the human subject—though not to the dereliction of the animal, whether as a type or as a source of experimental data illustrating the human. It might be improved by the addition of a few references to the major reviews and classical papers suitable for the more inquiring student, but the authors have clearly defined their task in the field covered, the treatment of it, and the size of the

volume. The book is well printed, and its illustrations are clear, refreshingly new, and in many cases excellent. It can be well recommended to the medical student as a supplement to his lectures, practical classes, and the bigger books.

A. ST. G. HUGGETT.

MUSCLE FUNCTION

Posture and Pain. By Henry O. Kendall, Florence P. Kendall, and Dorothy A. Boynton. (Pp. 204; 159 figures. £2 14s.) London: Baillière, Tindall and Cox. 1952.

The authors have set out the fruits of their long experience in evaluating muscle function, chiefly in cases of poliomyelitis. They have related these findings to postural defect in the healthy, whose different stances are effectively analysed. Good posture is defined as that satisfying the concept of standard skeletal alignment, and clear photographs show many different variations from the ideal. These include: high and low lumbar lordosis; flat back; kypholordosis; anterior position of the pelvis; scoliosis; unsatisfactory position of the scapulae, neck, and head; bow-legs; knock-knees; short calf muscles; rotated forefeet; and hammer-toes. The asymmetry dependent on handedness is well shown. No account is given of the postural deformities that arise from congenital disorders or from disease.

Analysis of muscle defect follows. The authors describe tests for muscle weakness, especially for distinguishing paresis of the lumbar muscles from that of the muscles about the hip. Illustrations also depict taut hamstrings limiting straight-leg raising, contraction of the ilio-psoas limiting hip extension, and short adductor muscles limiting elevation of the arm. The authors consider habits detrimental to good posture, and then the corollary—the prevention of deformities, including those to which amputees are liable.

Were the book to stop at this point it would command full agreement for its lucid account of established fact. But the authors then endeavour to discuss a number of ill-defined disorders of the trunk and limbs on the following assumption: "The basic thesis of this book is the importance of postural faults in disabling and painful conditions." No evidence is brought forward to support this hypothesis, though the authors admit that postural defect often exists without pain. Pain, they hold, is best alleviated by rectification of patients' postural faults, and go on to assume that this idea indicates that the emphasis in treatment falls on the muscles. Even if this theory is justified after poliomyelitis, so exclusive an attitude cannot be accepted as valid for ordinary persons. This criticism in no way reflects on the trustworthy methods of examination put forward, or on their effectiveness in identifying the source of a postural deformity.

J. H. CYRIAX.

TROPICAL DISEASES

A Handbook of Tropical Diseases: With Treatment and Prescriptions. By J. C. Banerjea, M.B.(Cal.), M.R.C.P. (Lond.), and P. B. Bhattacharya, M.B., D.T.M.(Cal.). Fifth edition. (Pp. 536; 23 figures. £2 2s.) Calcutta: U. N. Dhur and Sons. 1952.

This handbook is of limited scope and is obviously intended for use in India. No description is given of a number of diseases—for example, trypanosomiasis, undulant fever, yellow fever, yaws, schistosomiasis, tropical venereal diseases, tropical skin diseases, conditions peculiar to the hot countries of the Western Hemisphere, etc.—which are of great importance to practitioners in other parts of the Tropics.

Although it is claimed that this edition has been thoroughly revised and rewritten, many of the statements made are not in accordance with accepted modern ideas, and some of the recommendations are unfortunate. Only a few of these need be mentioned. Though corrected in the list of illustrations, in the chapter on malaria the exoerythrocytic cycle of development of the human parasite is shown as occurring in the reticulo-endothelial cells, and the decisive work of Shortt and his colleagues receives only the briefest passing mention. The dose schedule of "plasmoquine" recommended is 0.02 g. three times a day for seven days, followed by four days' rest, and then continued in the same dose for three consecutive days in a week for the next five weeks. This is a near toxic level, especially for dark-skinned races, and it is hardly surprising that the authors find that the drug frequently causes toxic symptoms. On the subject of the prevention of blackwater fever they state: "In the affected area the subjects of malarial infection should not avoid quinine, but should take it regularly and systematically in gr. 6 doses daily. The newer antimalarials paludrine, chloroquine, or camoquin in weekly doses will, however, give better protection." In fact, one of the decisive lessons of the war and subsequent years is that the avoidance of quinine and the substitution of one of the other antimalarials as a suppressant will virtually eliminate blackwater fever.

The chapter on amoebiasis is rambling and unbalanced. A long description of the signs and symptoms of the carrier (a term commonly confined to symptomless cyst-passers) differs little, if at all, from that given later, but more briefly, under the heading of chronic amoebic dysentery. It will startle the clinical pathologist to learn that acute amoebic dysentery should be investigated by making saline and iodine preparations of the stool and examining for cysts (this section is particularly garbled). On the subject of the diagnosis of rabies in dogs no mention is made of the all-important point that the dog should be kept in quarantine until it dies, and should not—other than in exceptional circumstances—be destroyed. Weil's disease is given as a synonym of leptospirosis, the variety of the disease caused by *Leptospira icterohaemorrhagiae* being the only one the authors recognize.

This book nevertheless contains much standard information and may prove of use to the students for whom it was written. It cannot be recommended to the general run of practitioners in tropical medicine.

J. S. K. BOYD.

PSYCHOLOGY AND THE SEXUAL CYCLE

Studies in Psychosomatic Medicine: Psychosexual Functions in Women. By Therese Benedek, M.D. (Pp. 435. $10.) New York: The Ronald Press. 1952.

This is the second volume of Studies in Psychosomatic Medicine from the Chicago Institute of Psycho-analysis—the first having been Alexander and French's *An Approach to the Cause and Treatment of the Vegetative Disturbances.* The first three-quarters of the book was previously published as a monograph of the National Research Council in 1942 by Benedek and Rubinstein. The basic information consisted in records of vaginal smears, basal body temperatures (152 cycles in 15 women), and psycho-analytic interviews of patients under psycho-analytic treatment by various psycho-analysts. Benedek discovered that she could correlate psychic content with phase of the sexual cycle. This is the first instance of the correlation of a normal physiological rhythm with the details of the changing psychic situations, modified, of course, by the personal, permanent, cultural attitudes. The final more general chapters on the psychosomatic implications of the mother–child unit, on the climacteric as a normal developmental phase, and on the general functions and disturbances of the sexual apparatus of both sexes are republications from various sources.

It is indeed interesting to have the experimental data republished along with more general and didactic chapters. The author does not set out to describe all the implications of sexuality in women, but she does describe basic problems and presents basic clinical and physiological material of value to gynaecologists, psychiatrists, and general practitioners, as well as suggesting further lines of co-operative research between physiologists and psycho-analysts. It is to be hoped that a time will come when such co-operative work can be repeated or elaborated in Britain.

W. CLIFFORD M. SCOTT.

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YESTERDAY AND TO-DAY

The Harben Lectures of the Royal Institute of Public Health and Hygiene were established to record progress in the field of public health, and those invited to give these lectures have in the past usually been men whose lives have been spent in research or in the application of preventive medicine. But last month saw a happy variation of this practice, when the Council of the Institute invited a distinguished clinician to give them the fruits of his wisdom, accumulated during more than fifty years' clinical experience. Lord Horder realized we are still close enough to the mid-point of the present century to justify his title of "Fifty Years of Medicine." Those who know him will rub their eyes when they learn that he qualified in 1896, a year after Röntgen's discovery of *x* rays and in the heyday of the bacteriological discoveries that revolutionized medical diagnosis and treatment. As Lord Horder puts it: "The present century, therefore, opened full of promise in the field of bacterial diseases, and the rapid progress was almost breath-taking." And so the story continues. To-day medicine is in another phase, or so it appears, of "breath-taking" progress, and we assume too easily that this is something peculiar to our own day. It is a wholesome corrective to be reminded by one of whom it was said that he "forsook the bench for the bedside" of the excitement of fifty years ago, to be reminded, indeed, that the progress has been continuous, the curve sharply accentuated at intervals in the stretch of years that go back to the date of Lord Horder's emergence on the medical scene. And his vast clinical experience adds point to his observation on modern methods of tackling bacterial infections, a field in which he made his own original contributions many years ago. "There is in this field such a wealth of available resources in treatment that the temptation to 'get busy' with one or more of the 'sulpha' drugs, or with one or other of the antibiotics, or, indeed, with one or other of both of these, before the nature of the infection is fully ascertained, is almost irresistible." Recent correspondence in these columns underlines the wisdom of this statement. Looking back on the early vaccine and serum treatment of infections, on Ehrlich's search for the *therapia sterilisans magna*, Lord Horder the clinician adds another wise saying: "But diagnosis is, after all, the alpha and omega of Medicine, and side by side with these slow advances in treatment came developments equally important, if less dramatic, in this sphere. The chief fillip came by the introduction of clinical pathology." It might indeed be said of him that he was the first clinical pathologist. As he has observed, he took "the bench to the bedside," and "Horder's box"[1] was in effect a new clinical instrument, the value of which others were slower to appreciate.

Two developments during the past fifty years are singled out by Lord Horder for special notice. One, the science of nutrition, he hails as "perhaps the most significant advance of all in the past half century of scientific medicine." Such a tribute from a clinician of Lord Horder's eminence must warm the hearts of those who feel, with the late Sir Jack Drummond, that practising doctors were slow to apply the lessons there to be learnt. Many will take courage from his remark that physical medicine is "one of the most important developments in Medicine in my time": though, as our correspondence columns have lately shown, not all would give it such a high place in a profession which has advanced so rapidly in so many diverse fields. If Lord Horder gives high praise to physical medicine, he tilts gently at the concept of "social medicine." "Humanist though I am," he said in his Harben Lectures, "and whole-hearted supporter of the thesis that Medicine should be made 100% available to the people, I have never been quite convinced that the notion underlying the new branch of it which has been called 'social medicine' has justified itself." Is there not here, perhaps, a confusion with what our American colleagues call "socialized medicine"? And has social medicine had time to "justify itself"? Lord Horder believes that the Institute of Social Medicine at Oxford has recently come under the auctioneer's hammer "because others than myself do not regard the segregation of 'social, genetic, and environmental factors in the incidence of human disease and disability'—to quote its governing phrase—as helpful in the general advance of Medicine." Meanwhile, Cambridge goes quietly ahead by consolidating the position of its department of human ecology—a more exact and less provocative designation than the term social medicine.

When the Harben Lectures are published many will want to read them and to digest their wisdom. Here it has been possible to comment upon only one or two of the many themes touched upon. "Nursing is a part of medicine." "How long a man lives depends upon his ancestors, the state of the public

[1] *British Medical Journal*, 1951, 1, 31.

hygiene and, we must now add, dictators. How healthily and how happily he lives depends upon himself." These and many other *obiter dicta* show that Lord Horder has inherited the gift of pithy statement from his teacher Samuel Gee. If he tilts at what may be passing medical fashions, he makes an extra vigorous thrust at the Health Service: "The new scheme was based primarily upon the hospital and not upon the family physician—the G.P., as we all call him." Much of his third lecture was on this theme, and his own reply to his own question, "Shall we ever recover?" is, "Of course we shall." The background of his philosophy is shown by his belief in the value of the eugenic approach to the problems of society. "All it means is that, in the view of the eugenist—a view which I share with utter conviction—the economic advantages, using the term in its widest sense, lie with efforts made towards racial betterment rather than with social service in a particular generation." The Harben lecturers of the future will find in Lord Horder's valuable contribution ready texts for their discourses.

RHEUMATIC CARDITIS

Attractive as it certainly is, the allergic hypothesis of rheumatic carditis still lacks the sort of evidence which would explain the confusing natural history of this perplexing disease. Why, for instance, is it so infrequent a complication of the convalescence from acute streptococcal pharyngitis? Why is there no correlation between the severity of the initial angina and the intensity of the carditis? Why is the heart the chief and often the only shock organ? These problems were discussed, and the allergic hypothesis defended, by Professor Geoffrey Hadfield in his Carey Coombs Memorial Lecture delivered in Bristol on December 2. He pointed out that the comparatively long delay between the onset of the sore throat and the establishment of the acute rheumatic state is so constant and characteristic a feature that the carditis, if allergic, more closely resembles delayed serum sickness than any other allergy. On this supposition it is justifiable to assume that the first event in the pathogenesis of the carditis is fixation of a streptococcal antigen on the surface of cells of the cardiac tissues and its simultaneous absorption either by the whole reticulo-endothelial system, if the antigen is blood-borne, or by some integral part of it, a group of lymph glands, for instance, if lymph-borne. At the end of the latent period of about 10 days antibodies reach the heart and the encounter between them and the cell-fixed antigen in the cardiac tissues causes injury and necrosis of the antigen-carrying cells. Toxic vasodilator amines and possibly polypeptides are liberated from these injured cells and rapidly produce capillary paralysis and plasma exudation. In the wake of this sudden and violent "triple response" small scattered cellular foci of proliferating fibroblasts and histiocytes appear, their growth being stimulated by the autolysing remains of cells killed in the initial onslaught.

If the original pharyngeal angina is due to a pyogenic streptococcus it is impossible, as Professor Hadfield said, to escape the conclusion that the inflammatory exudate would be copious and would drain into the cervical lymphatics. For a few hours at least the volume of lymph flowing into the main jugular lymph trunk would quite probably amount to about 10 times the volume of the normal flow. Its protein content would be increased, and it would in all probability contain in high concentration antigenic and possibly allergenic split-products resulting from the disintegration of streptococcal cells. Some of these antigenic split-products would presumably be arrested in the cervical lymph nodes, where antibodies would almost certainly be produced to them. In the early stages, therefore, the jugular collecting trunk would contain a high concentration of streptococcal antigen and some 10 days later a high and rising concentration of antibody. It is tempting to assume that in those children who develop carditis following a streptococcal sore throat the inflamed pharynx and the cardiac tissues are linked together by a direct lymphatic pathway. At first this would carry antigen directly to the heart and after 10 days or so would convey its appropriate antibody. To postulate a retrograde lymph flow from the jugular into the mediastinal lymph trunk may be regarded as an ingenious variant of the ancient device of begging the question, but the idea has something to commend it. It postulates precisely that kind of localized, limited lymph-borne infection which so often favours the establishment of an allergic state. It would explain why the heart receiving the bulk of the antigen becomes the predominant shock organ when its sensitized tissues receive the bulk of the antibody. Anatomical considerations lend some support. The termination of the jugular, subclavian, and mediastinal lymph trunks in the great veins at the base of the heart is notoriously irregular, and in a small percentage of human beings the jugular trunk carrying pharyngeal lymph is said to unite with the mediastinal trunk carrying cardiac lymph before they open by a common trunk into the innominate vein.

Histological research carried out by Murphy[1] at the Rockefeller Institute in New York suggests that

[1] *J. exp. Med.*, 1952, **96**, 319.

current views on the evolution of the submiliary nodule of Aschoff may be not only erroneous but misleading. The evidence he submits suggests that the initial cellular injury falls upon the muscle cells of the heart. Some of these cells are killed, and it is the necrotic remains of their sarcoplasm which excite the focal histiocytic and fibroblastic response. Murphy claims that the fragments of acellular material seen in the early Aschoff nodule are not degenerate collagen but slowly autolysing sarcoplasm. In some muscle cells the sarcolemmal nuclei survive the injury, and in a valiant but fruitless attempt to regenerate muscle cells they proliferate in small fragments of sarcoplasm to produce the familiar Aschoff giant cell, which, according to Murphy, is really a multinucleate myoblast. These careful observations, supported by excellent pictorial evidence, are in opposition to the fashionable conception that the initial injury is on the collagen framework of the heart. Murphy finds that a limited amount of newly formed collagen appears in the lesion in its later stages but regards this as a purely secondary phenomenon. His views, if proved to be correct, lend some support to the allergic hypothesis of rheumatic carditis, for antibodies and antigens show some proneness to unite on the surface of involuntary muscle cells—those, for instance, of bronchiolar muscle in spasmodic asthma, those of uterine muscle in anaphylactic shock, and, with less certainty, the cells of intestinal muscle in the food allergies and of arterial muscle in allergic arteritis.

AN INHIBITOR OF MORPHINE

A substance (N-allylnormorphine hydrobromide) is now available which can be used to counteract the effect of an excess of morphine, whether too large a dose of morphine has been given or whether a patient has reacted excessively to a normal dose. The substance is closely related in chemical composition to morphine itself, in which there is a nitrogen atom with a methyl group attached. By simple substitution of this methyl group by an allyl group a morphine antagonist is obtained. In having a weak analgesic action and also a depressant effect on respiration it acts like morphine, but its main therapeutic interest lies in its power to combine with the receptors on which morphine acts so as to prevent or to reverse the action of that drug. If, for example, a dog is injected with a large dose of morphine, in about 20 minutes it is prostrate, almost fully narcotized and salivating: it cannot be aroused. If an injection of N-allylnormorphine is given, within 10 minutes the dog stands up, runs about, and behaves normally. Or again the action can be seen in animals such as monkeys which have received daily doses of morphine and are addicted to it. The injection of N-allylnormorphine produces in a few minutes the symptoms of morphine withdrawal: the monkey lies down on its belly with griping abdominal pain.

In 1915 Pohl[1] stated that a related substance, N-allylnorcodeine, while almost inactive itself, antagonized the respiratory depression due to morphine. N-allylnormorphine was first made in 1941 by McCawley, Hart, and Marsh[2] and has been studied by many workers since that time.[3-5] Not only does it reverse the effect of morphine itself but also that of other analgesics such as methadone ("physeptone") and pethidine; it is, however, inert against barbiturates or against anaesthetics like ether and cyclopropane.[6,7] N-allylnormorphine has been used effectively to increase the rate and depth of respiration in patients who have received excessive doses of morphine (up to 90 mg. or 1½ gr.) and of pethidine (600 mg.).[6] The amounts given were from 5 to 10 mg., and the effect was to double or treble the respiration rate and the respiratory minute volume. A second injection was less effective, and a third usually ineffective. The heart rate was slowed; and blood pressure was raised when it was subnormal, but not otherwise. Larger doses raised the blood pressure in all cases.[8]

N-allylnormorphine has been used to counteract depression in newborn babies when narcotics, such as pethidine, have been given to the mother.[8] On several occasions when the baby failed to breathe or was cyanosed the injection of 0.1 mg. into the umbilical vein caused respiration to begin within one minute. Effects of the drug itself in man seem not to be serious except in morphine addicts, in whom it produces withdrawal symptoms.[9] In those who were formerly addicts N-allylnormorphine in doses from 30 to 75 mg. caused drowsiness, vivid daydreams, and alarm varying from vague anxiety to panic.[10] When given to normal subjects there was little effect, save a depression of respiratory minute volume; there was no nausea and no effect on heart rate and blood pressure.[6]

1 *Z. exp. Path. Ther.*, 1915, **18**, 370.
2 *J. Amer. chem. Soc.*, 1941, **63**, 314.
3 Unna, K., *J. Pharmacol.*, 1943, **79**, 27.
4 Hart, E. R., and McCawley, E. L., ibid., 1944, **82**, 339.
5 Smith, C. C., Lehman, E. G., and Gilfillan, J. L., *Fed. Proc.*, 1951, **10**, 335.
6 Eckenhoff, J. E., Elder, J. D., and King, B. D., *Amer. J. med. Sci.*, 1952, **223**, 191.
7 Huggins, R. A., Glass, W. G., and Bryan, A. R., *Proc. Soc. exp. Biol. (N.Y.)*, 1950, **75**, 540.
8 Eckenhoff, J. E., Hoffman, G. L., and Dripps, R. D., *Anesthesiology*, 1952, **13**, 242.
9 Wikler, A., Carter, R. L., Fraser, H. F., and Isbell, H., *Fed. Proc.*, 1952, **11**, 402.
10 —— ibid., 1951, **10**, 345.

LEGAL RESPONSIBILITY FOR MISTAKES

An article in a German medical journal has recently discussed the events which led to a court in Lübeck sentencing a doctor to a fine of 1,500 D.M. for causing the death of a patient.[1] The circumstances were unusual. There appeared in an issue of a medical journal a description by a reputable authority of a treatment for pruritus ani by subcutaneous injections of alcohol. The author recommended local analgesia by infiltration with "nupercaine" (cinchocaine). The quantity of solution was specified, and twice in the article the strength of the solution was given as 1%. This was a

1 Malorny, G., *Samml. Vergiftungsf.*, 1952, **14**, 40.

misprint for 0.1%, as the following week's issue of the journal hastened to point out. The doctor, who for eight months had been treating an intractable case of pruritus ani in a 28-year-old patient, read the article. Unhappily he did not read the correction of the misprints in the following issue. He decided to try the treatment, and ordered 1% cinchocaine from the Lübeck dispensary, relying upon the accuracy of the article. The patient died from an overdose of cinchocaine before the alcohol injection was started. It was only after the patient's death that the doctor realized on consulting a textbook that the solution had been 10 times too strong. The fatal failure to see the mistakes in the article can be said to have been shared by its author, who presumably had the proofs to correct, possibly the publishers, the dispenser, and the doctor himself. German law fixed the doctor with criminal responsibility.

Had the same train of events occurred in England no criminal proceedings would have been brought. To cause death by negligence does not amount to the crime of manslaughter unless the person concerned has shown a reckless disregard of the life and safety of others. A mistake, while it may give rise to civil liability, does not in English law attract criminal responsibility unless it is so gross as to fall within that criterion. No prosecuting counsel would ask an English jury for a verdict of manslaughter on the facts of the Lübeck case. There remains the question of civil liability. In English law if someone owes a duty to another to take reasonable care in his activities towards him and in breach of that duty fails to take reasonable care, with the result that the other suffers damage, he is civilly liable to pay damages to the other to compensate him for the harm he has suffered. Where as the result of the breach of duty the harm the other suffers is death, his personal representatives are entitled to recover damages for his loss of expectation of life, and on behalf of his dependants for the loss of the breadwinner on whom they depend. In English law the author of the article and the publishers would not be civilly responsible on the ground that it was not their mistake which caused the death but the intervening act of the doctor in giving the injection. The dispenser would not be liable, because his duty is to give the doctor what the doctor asks for. Whether or not the doctor would have been held to be civilly responsible in the English courts is a problem which it is less easy to answer. He undoubtedly owed a duty of reasonable care in his professional activities towards his patient. The patient undoubtedly suffered death, which the law regards as damage, as a result of those activities. The question for the court would be, did he in all the circumstances of the case take the amount of care a reasonable doctor would have taken? As in all cases of medical negligence the judge, and the jury if there is one, would not be able to answer this question without hearing the opinion of expert medical witnesses. It is not a breach of the duty to take reasonable care if a doctor does what is generally considered by the profession to be a proper thing to do having regard to the state of medical knowledge at the time he does it, even if a subsequent advance in medical knowledge shows it to have been hazardous in the extreme. It really comes in the end to this: Would a careful, competent doctor unfamiliar with nupercaine have relied on the dosage stated in the article without reference to a textbook or to a colleague who was familiar with the drug? If the answer is no, in English law the doctor is civilly responsible.

ANTIDOTES FOR CYANIDE

Antidotes for poisons have a dramatic interest, but often in practice—by the time they are remembered, located, and administered—the poison has exerted its lethal effect. Added to this is the suspicion that many of the antidotes are of dubious efficacy. It is therefore of some interest that an enthusiastic account of the use of nitrites and thiosulphate as antidotes in cyanide poisoning, usually regarded as particularly deadly, has recently been published.[1]

Treatment with nitrites and thiosulphate has been recommended in standard textbooks for many years. On the basis of 20 years' experience, Chen and Rose, the authors of the latest report, recommend the inhalation of amyl nitrite and the intravenous injection of 10 ml. of 3% sodium nitrite and 50 ml. of 25% sodium thiosulphate. This course of treatment was derived from the experimental finding that the minimum lethal dose of cyanide for dogs could be raised 18-fold if followed immediately by the combined nitrite and thiosulphate therapy. The combination of nitrite and thiosulphate was more effective than either antidote when administered alone. In confirmation of this experimental work the authors quote the excellent results of treatment of human cases of cyanide poisoning with nitrite and thiosulphate. Their presentation of the data is, however, insufficiently objective to allow a critical assessment of the value of treatment, since many of the cases reported were given only part of the treatment, and in others treatment was begun more than two hours after poisoning and could have had very little effect on recovery. Chen and Rose state that since the nitrite and thiosulphate treatment has been used 44 cases have been treated, with 43 recoveries. These 44 cases have been selected from the literature of two continents over a period of 18 years. During part of this time (1933–48) in the United States alone 248 people died of accidental cyanide poisoning, and suicides totalled more than 3,000. It is difficult to believe that none of these cases were given antidotes that could be found described in standard textbooks of the period. There is a natural tendency to record successful treatment and leave the failures unpublished. It is doubtful if a survey of the literature gives anything but a group selected for success.

Despite this criticism there is much of value in Chen and Rose's paper. The good response to nitrite and thiosulphate which they describe has also been observed

[1] *J. Amer. med Ass.*, 1952, **149**, 113.
[2] *Arch. Industr. Hyg.*, 1951, **4**, 417.
[3] *Brit. J. Industr. Med.*, 1950, **7**, 125.
[4] Halstrøm, F., and Møller, K. O., *Acta pharmacol.* (*Kbh.*), 1945, **1**, 18.

by Wolfsie[2] in the United States and by Potter[3] in this country. The experience of these writers is that where treatment can be started immediately most victims can be resuscitated. The successes in treatment have mostly been obtained in factories, where the risk of poisoning is clearly recognized and the workers themselves have played a crucial part in treatment. An essential precaution is the education of the workers in the risk of poisoning and in the need for immediate action. Rescue procedure must be practised; this consists in removing the patient from the contaminated area, immediate artificial respiration if breathing has ceased and continuation until breathing is fully established, removal of contaminated clothing, and the washing of contaminated skin with soap and water. All these things must be done in the minutes that are passing while the first-aid kit is being collected and the doctor and ambulance called. The solutions of nitrite and thiosulphate must be available for immediate injection. The dread reputation of cyanide rests less on its toxicity—which at 0.7–3.5 mg. of absorbed cyanide per kilo body weight in fatal cases[4] is not outstandingly high—than on its speed of action. When large doses are absorbed the patient falls unconscious in a few seconds, but in most cases of poisoning several minutes elapse before any effect is noticeable, and death occurs within 15 to 60 minutes. This is sufficient time for a well-drilled team with equipment close at hand, but without such organization victims of poisoning will die before skilled attention can be given and antidotes administered. This is reflected in the figures for cyanide poisoning in this country for the period 1940–9: in 10 years there has been only one occupational death among employees of firms handling cyanide, whereas there have been 32 other accidental deaths.

THE CLIMACTERIC AND OESTROGEN THERAPY

The climacteric in the female is a regressive phase of life occupying a period of years in which the actual cessation of menstruation is but a landmark. Nevertheless the terms climacteric and menopause are commonly used synonymously. At this period of life three out of every four women experience to some degree certain subjective symptoms of which the hot flush is the most characteristic. The primary cause of the menopausal syndrome, as it is sometimes called, is ovarian failure, but most of the symptoms are not due directly to this but rather to a secondary disturbance, operating through the pituitary gland, of the whole endocrine balance and of the closely linked autonomic system. The ovarian failure can be countered by oestrogen therapy, and indeed each year brings new commercial preparations of synthetic and natural oestrogens which are advocated for the relief of menopausal symptoms. Most recently the superior merits of combining oestrogen with androgen for this purpose have been widely publicized. The two hormones are in many ways complementary and synergistic in their actions, but they do not neutralize each other, and when given together undesirable side-effects of both may appear simultaneously—vaginal bleeding alongside hirsutism and hoarseness. Unfortunately the claims made for some of the new hormone preparations have been more enthusiastic than discreet, and the range of symptoms, often in fact coincidental, which are claimed as indications is being increasingly widened. In addition, with little or no change of proprietary name, oestrogen has been added to the formula of preparations previously free of hormones. And, as oestrogen is readily absorbed through the skin, the use of skin creams containing only minute amounts may cause undesirable side-effects. One practical consequence of all this is that oestrogen medication, sometimes without the patient or doctor being aware of the exact constitution of the prescribed medicine, is becoming one of the commonest causes of post-menopausal bleeding. This is not to deny that in women extremely sensitive to the hormone vaginal bleeding may be a consequence of treatment correctly given and properly controlled, but it does suggest that the temptation to resort to oestrogens as a first line of treatment is found difficult to resist. It should not be.

It has been said that so far as feminine tradition is concerned "the change" is invested with more horrifying stories than either childbearing or operations. But the effect of the climacteric on the individual woman varies with the inherent stability of her temperament, her education, and her environment. In only about 20% of women are menopausal symptoms severe. In the majority simple explanation of cause and significance, due emphasis on the temporary nature of the upset, and repeated reassurance to counter the common feeling of insecurity are sufficient. The general practitioner with his intimate knowledge of family and background is in a uniquely favourable position to offer such sympathetic assistance at this critical time. In many cases the judicious prescription of mild sedatives also helps. In a minority, probably less than 10%, in whom severe discomfort persists despite these measures, oestrogen therapy is indicated with the object of tiding the patient over the period of adjustment. If this is to be achieved without side-effects troublesome to the patient and without irregular bleeding worrying to the doctor, certain principles should be observed. Strict instructions about dosage are necessary, otherwise the patient may resort to an occasional tablet when unwell or unhappy and so develop an oestrogen resistance. The oestrogen of choice should be given orally and in the smallest dose which just fails completely to relieve all symptoms. It should be administered for 21 consecutive days out of 28, thus simulating the normal cycle, and treatment should not be discontinued suddenly but gradually tapered off over three to four months. Any abnormal bleeding which accompanies or follows treatment must not be regarded as consequential, but the patient should be referred for full gynaecological examination, including curettage. Indeed, where there is a strong family history of genital cancer, or where the menopause was induced by surgery or radiotherapy for gynaecological carcinoma or endometriosis, oestrogens are probably best avoided.

REFRESHER COURSE FOR GENERAL PRACTITIONERS

HEAD INJURIES—I. BRAIN INJURY AND ITS DIAGNOSIS

BY

D. W. C. NORTHFIELD, M.S., F.R.C.S.

Surgeon-in-Charge, Department of Neurosurgery, London Hospital

Injuries of the head derive their seriousness largely from the degree to which the brain has been damaged or may subsequently suffer damage by complications. The brain may sustain concussion, contusion, or laceration ; it may be gradually compressed by an effusion of blood ; or it may become the seat of inflammation if infection invades the cranial cavity as a result of the injury providing a portal of entry. The only importance of fractures of the skull, if not compound or depressed, is that they give some indication of the severity of the impact.

The diagnosis of the nature and extent of the brain injury, and of the presence or otherwise of complications, such as compression of the brain, rests essentially on the clinical picture.

Concussion

Concussion of the brain is characterized by the immediate cessation of consciousness after a blow on the head. If examined within a few moments of the injury the patient will be found to be profoundly unconscious, pale, and to have a slow feeble pulse and shallow respirations ; the limbs will be flaccid ; and all reflexes, such as the pupillary, corneal, tendon, and plantar, will be unobtainable. If the blow was not severe this state will rapidly resolve and within a few minutes the patient will be fully conscious and the vital activities and all reflexes will be normal. It is now generally accepted that concussion is a reaction of the nerve cell to certain physical stresses which is characterized by immediate paralysis of its function, with minimal or no structural damage, and a natural tendency to rapid recovery. This is in keeping with Trotter's classical definition: "An essentially transient state due to head injury which is of instantaneous onset, manifests widespread symptoms of purely paralytic kind, does not as such comprise any evidence of structural cerebral injury, and is always followed by amnesia for the actual moment of the accident."

Experimental work carried out in recent years shows that the brain is most readily "concussed" by a force which causes abrupt acceleration—when a rapidly moving object strikes the stationary head—or deceleration—when the falling head strikes the ground. If the head does not move but is suddenly crushed, as in shunting accidents, consciousness is often retained in spite of extensive fracture of the skull. A much greater force must be expended in order to cause "compression" concussion as compared with "acceleration" concussion. The energy dissipated in producing concussion is usually supplied by a blunt or smooth-surfaced heavy object ; if the force comes from a small rapidly moving object, such as a bullet, the energy is dissipated in penetrating the skull, causing only local damage to the brain. Provided the missile does not damage vital centres, consciousness is often retained, the reason being that insufficient acceleration has been imparted to the brain to bring about the diffuse neuronal disturbance responsible for concussion.

Contusion and Laceration

In addition to the diffuse disturbance of neuronal function called concussion, injury may, and often does, bring about structural brain damage. Necropsy reveals haemorrhages, petechial or coarse, subpial or within the substance of the brain, scattered diffusely or localized to the several poles of the brain. Microscopical examination shows areas of structural damage to the nerve cells and their tracts, and to small and large blood vessels ; areas of glial reaction to this tissue injury will be found if some hours have elapsed before death. The term "contusion" is given to such breaches of anatomical continuity. When the damage is more severe naked-eye examination may reveal laceration and dissolution of brain tissue and extensive haemorrhage. Contusion, laceration, and haemorrhage may be found immediately under the site of impact, particularly if there is a fracture of the overlying skull ; or the damage may be at a remote part of the brain, and then constitutes contre-coup injury. These coarse lesions of the brain arise as a result of the sudden distortion of the skull, with or without fracture, brought about by the impact, and of the various shearing stresses imparted to the brain, which tends to swirl about within the cranium. Such physical stresses will be prominent where the poles of the brain are brought in contact with the buttresses of the cranium—for example, the temporal poles against the sphenoidal ridges—and where such movement is restricted by the great dural partitions. the falx and the tentorium,

It is not clear yet to what degree the coarse lesions of brain injury affect recovery from concussion. It is quite certain that contusion may occur without concussion : delayed symptoms of headache, dizziness, sleeplessness, and lack of concentration may arise after a glancing blow on the head which does not cause loss of consciousness. If the unconsciousness of concussion is a transient functional disturbance, then the prolonged coma and slow recovery after severe head injury may be regarded as the result of structural brain damage. Whether or not slowness of recovery of consciousness is due to contusion, it is certain that many of the permanent residual disabilities are due to the structural brain damage. Impairment of intellect and personality changes may follow widespread bifrontal contusion, and hemiparesis, dysphasia, hemianopia, etc., will result if there has been extensive tissue injury in the anatomically appropriate areas of the brain.

Compression of the Brain

The essential injury of the brain, be it concussion, contusion, or laceration, produces a clinical syndrome in which there is a strong tendency towards recovery. Provided the vital centres are not irreparably damaged and complications do not develop, and provided treatment is along correct lines, there should be a gradual and steady improvement in the patient's condition. To this picture, produced by the immediate brain damage, Jefferson has applied the term "basic state." The value of this conception resides in its emphasis on the word "basic," from which datum line one can take measurements of improvement or of deterioration. This implies observation over a period of time during which symptoms and signs may develop, indicating the presence of complications, the most important of which is compression by blood. Jefferson emphasizes the importance of such fresh developments by calling them "epiphenomena."

Injuries of the skull, either by fracture or by distortion, may tear meningeal vessels, usually the middle meningeal ones. Haemorrhage occurs between the dura mater and the skull and gradually separates the membrane from the bone, the brain being compressed during this process. The rapidity of the bleeding is such that an extradural haematoma manifests itself usually within 6 to 24 hours of the accident and if unrelieved by operation it swiftly kills. Bleeding may also occur into the potential space which

exists between the dura mater and the arachnoid, forming a subdural haematoma. The bleeding arises from veins passing from the cortex to the large dural sinuses; it is often bilateral, and the blood, which for the most part remains unclotted, spreads diffusely over the convexity. The haematoma increases in size more slowly than the extradural variety and manifests itself somewhat later. If the quantity is small its presence may evade detection for weeks, particularly if the head injury was trivial, and it then tends to encapsulate itself by membrane formation; in such cases, and in elderly subjects in whom it is prone to occur, the head injury may be forgotten and compression of the brain by a chronic subdural haematoma may then simulate cerebral thrombosis or tumour. A similar condition can occur in infants, causing enlargement of the head, and may be mistaken for hydrocephalus.

Cerebral laceration usually causes an effusion of blood into the subarachnoid spaces, and sometimes into the ventricles. Such bleeding rarely of itself leads to compression of the brain. Laceration severe enough to cause a serious degree of subarachnoid or ventricular bleeding is usually fatal because of the intrinsic brain damage. Intracerebral haematoma, other than in rapidly fatal injuries, is relatively rare. It may arise from focal laceration and vessel damage, or it may occur as a sudden event some days after the accident, the so-called *spät apoplexie*.

As a result of cranial distortion the arachnoid may tear, allowing cerebrospinal fluid to seep into the subdural space. Owing to the poor rate of absorption of liquids from the subdural space, the cerebrospinal fluid may collect in quantities large enough to compress the brain. It is then called a "subdural hydroma"; it is generally of slow development and is clinically indistinguishable from subdural haematoma.

Fractures of the Skull

As with fractures of other bones, skull fractures may be closed, when the overlying skin is not broken, or open (compound), when the fracture line communicates with the external air through a wound. The importance of this classification is precisely the same as that in other bones—the risk of infection if the fracture is open. A fracture of the frontal bone which appears closed, there being no overlying scalp wound, may nevertheless involve the posterior wall of the frontal sinus or the roof of the nose, and thereby tear the mucosa; in this way it is in fact open. A fracture of the middle cranial fossa which involves the middle ear is similarly open. The intact dura mater underlying an open fracture forms a good barrier against infection, but if the injury has also torn the dura mater a penetrating infection may lead to meningitis and even to brain abscess. This is particularly prone to occur in fractures involving the frontal sinus or roof of the nose, with tearing of the dura mater, and such fractures may easily pass unrecognized; a flow of cerebrospinal fluid from the nose (or from the ear in a case of fracture of the middle fossa) is of course pathognomonic.

In addition to being open or closed, a fracture may be fissured or comminuted. It may not alter the normal contour of the skull, or the force of the impact may cause depression of fragments. In children a depressed fracture often occurs without laceration of the overlying skin, but in adults the skin is usually broken. The area of damaged bone may form a saucer-like depression, or individual fragments may be so tilted and so pointed as to tear the dura mater and to damage the underlying brain. In severe injuries, and with missiles, the bone fragments may be projected fanwise into the brain. Depressed fractures compress the brain in the immediate locality, but if symptoms of generalized brain compression develop they are usually due to an accompanying extradural or subdural haematoma.

Scalp Wounds

Lacerations of the scalp may vary from minor superficial abrasions to extensive and complicated wounds. They may be widely contused or cleanly incised. There may be avulsion of flaps. Serious loss of blood may occur from a scalp wound, and cause shock which may disguise the basic state. What may be regarded as "only a scalp wound" may in fact be an open fracture. Damage to underlying brain, a focal contusion, may be present in addition to the scalp wound, whether or not there is a fracture of the skull; thus a scalp wound on one side of the head, without any fracture of the skull, may be associated with a weakness of the opposite arm or leg.

Cranial Nerve Palsies

In addition to the injury sustained by the brain, the individual cranial nerves may be damaged between their points of emergence from the brain and their foramina in the skull, or in those foramina. The paralysis may be transient, of long duration, or permanent, according to the degree of damage and to the particular nerve involved.

Injury to one or both *olfactory nerves* often occurs in frontal-lobe contusion, and particularly when the impact is received on the forehead or the occiput. The sense of smell may be partly or completely lost, at one or both nostrils. If the anosmia is absolute, appreciation of flavour is also impaired. The disability is potentially serious, because the patient is unaware of the smell produced by a leak of gas or by petrol. A perverted sense of smell—parosmia—or olfactory hallucinations may sometimes occur.

One or both *optic nerves* or the *optic chiasma* may be injured; bizarre abnormalities of the visual fields may be detected, according to the site and degree of the lesion, or vision may be completely destroyed. There is rarely any accompanying fracture of the optic foramen, although a fracture through the floor of the anterior fossa may be evidence of the severity of the force involved. Loss of vision will not be revealed till full consciousness is gained, but if one optic nerve is severely damaged the pupil of that eye will not react to direct light stimulus, and the significance of such a single abnormal sign may not be immediately appreciated. Primary optic atrophy will develop after several weeks, confirming the nature of the injury.

The motor *nerves of the eyeball*—the oculomotor, the trochlear, and the abducens—may be injured within the cranium or more often within the orbit as a result of severe bruising, commonly due to fracture of the wall of the orbit. The intraorbital bleeding may produce proptosis. Disturbances of the pupillary reactions and squints will occur. Such signs may also be caused by damage to the nuclei in the brain stem.

Damage to sensory branches of the *trigeminal nerve* usually occurs only as a result of fracture of the facial skeleton. Paralysis of the masticatory muscles is very rare.

The *facial* and *acoustic nerves* may be involved in a fracture of the petrous bone. Damage of the vestibular portion of the eighth nerve may give rise to vertigo. Injury of the other cranial nerves does not occur except as part of a fatal injury.

Diagnosis

Loss of consciousness is an essential feature of concussion, and for this period of time there is complete loss of memory. If the patient has already regained consciousness when the doctor arrives concussion can be assumed to have occurred if there is no recollection of the actual injury. If return of full consciousness is delayed for more than a few minutes, if abnormal neurological signs persist for more than 24 hours, or if there are signs of a coarse lesion of the brain—for example, monoparesis or hemiparesis, etc.—then the basic state indicates structural damage—namely, contusion (with or without laceration). Consciousness may not return for hours or days, and the patient passes successively through periods of stupor and mental confusion, and intermittent periods of full and clouded consciousness, until the normal is reached. There may be stages of mental and physical excitement, with resistance to nursing care—so-called irritability, which should be more accurately regarded

as being due to paralysis of the higher inhibitory mental processes. Incontinence of urine and faeces may occur, or retention of urine may aggravate restlessness. Fever, neck stiffness, and a positive Kernig's sign indicate irritation of the meninges by blood. Such signs will also develop if meningitis occurs, and the possibility of infection spreading through a hidden basal fracture must be borne in mind. Persistent headache, vomiting, and giddiness are common symptoms of brain contusion and, as pointed out earlier, may occur without loss of consciousness—that is, without concussion. The pulse rate is commonly raised for a day or so after brain contusion, and then is often succeeded by a bradycardia about the fourth day lasting for some days. The temperature may rise to 103° F. (39.4° C.), or even higher, within a few hours of a brain injury, although occasionally the injury is so severe that a pyrexial reaction does not occur; the thermo-regulatory mechanism is paralysed and the temperature falls; such injuries are commonly fatal.

When confronted with a case of head injury the presence of concussion with or without contusion may be self-evident; but a common difficulty is to decide whether the patient is also suffering from another disease or intoxication which may have caused him to fall and stun himself—for instance, epilepsy, acute alcoholism, uraemia, diabetes, or cerebral haemorrhage from atheroma or aneurysm. An account of the accident given by an eye-witness may be of great value; examination of the exterior of the cranium may reveal ample evidence of a severe injury. Information from relatives or the doctor's own knowledge of the past history of the patient may clarify the possible importance of non-traumatic causes of coma.

In every case of head injury the problem arises whether there is cerebral compression or whether it is going to develop later. An unpredictable period of time must elapse after the injury before compression of the brain can occur. Consequently, immediately after an injury *no one* can predict whether or not compression will occur. If the concussion is brief and consciousness rapidly returns, the symptoms of compression, the epiphenomena, will be more easily recognized. As the clot enlarges, the fully conscious patient complains of increasingly severe headache, he may vomit, and consciousness becomes clouded and is finally lost. But if the brain injury is severe there may be no lucid interval—that is, consciousness is not regained but gradually deepens as compression progresses, and the most critical observation is necessary in order to detect this change at the earliest moment. Accompanying the recurrence or the deepening of unconsciousness will be found fresh neurological signs of a paralytic order. The pupil on one side (usually the side of the bleeding) becomes dilated and fixed (non-reactive to light) and the other pupil later follows suit. The opposite limbs become paralysed, their tone abnormal (sometimes spastic and sometimes flaccid), the tendon reflexes increase, and the plantar response becomes extensor. If the compression is not relieved the limbs on both sides become paralysed, and the patient may finally present a state of decerebrate rigidity with bilateral extensor plantar responses. Respirations become deep, laboured, and stertorous, and may terminally show Cheyne-Stokes rhythm; the patient's face is congested. Occasionally increase of blood pressure and a bradycardia may occur as cerebral compression develops; more commonly, however, little change occurs in the blood pressure after the patient comes under observation, and the pulse rate steadily mounts.

The crux of the matter lies in the repeated observation and recording of the patient's condition in order to detect at the earliest moment any deterioration of, or deviation from, the basic state. Where coma persists without improvement, or where abnormal signs lead to suspicions of the presence of a compressing lesion, it is advisable to make certain of the diagnosis by exploratory operation. This comprises the drilling of small burr-holes or trephine-holes over appropriate areas of the cranium; it should be done under local analgesia, and causes little disturbance of the patient. It may prove a life-saving measure and should not be unduly deferred, for when compression has developed the patient's condition may worsen with incredible rapidity. Whether the haemorrhage is extradural, subdural, or intracerebral is of more moment to the surgeon who has to deal with the case. The time of onset of the change in the patient's condition, the rapidity of deterioration, the crispness of localizing signs or their diffuseness and insidious march, and the presence of local scalp or skull damage, all may help in locating the site of bleeding.

[Part II will appear in our next issue.]

Refresher Course Book.—The first 55 articles of this series (fully revised) are available as a book, price 25s., from the Publishing Manager, B.M.A. House, Tavistock Square, London, W.C.1.

Nova et Vetera

EARLY CONTRACEPTIVE SHEATHS

During a recent examination of the contents of a muniment room in a large English country mansion a locked box was discovered which, on being opened, was found to contain a number of sheaths of an early type. They were in packets of eight, of three different sizes, and the inner (white) and outer (blue) wrappers were apparently those in which they had been delivered.

Some of these sheaths were brought to me at the British Museum for examination and report. The specimen submitted is apparently made from some animal membrane, and as far as could be discovered is seamless, the edge of the open end being turned over and roughly stitched with cotton to form a hem through which is threaded a strip of silk. Its approximate dimensions are: length, 190 mm.; diameter, 60 mm.; thickness, 0.038 mm. (as compared with the thickness of a modern thin rubber sheath of 0.075 mm. The membrane was found to be permeable to water and to a solution of salt and water. Both white and blue wrappers were made from rag and neither showed any watermark, the chain and laid lines being clearly visible; the blue colour of the outer wrappers was due to indigo.

If it be true, as is held by some authorities, that the appearance of a piling up of the pulp beside the chain lines (which is present in the white wrapper) indicates a date of manufacture probably prior to 1800, then this, with other features in the case, suggests that the date to be assigned to these sheaths is between about 1790 and 1810.

Although the inventor of the contraceptive and preservative sheath is still unknown, in spite of the attempts to prove that he was Colonel Condon or Cundum living in the reign of Charles II, much has been recorded about it in later times, especially in the eighteenth century. At that time skin sheaths were often used, and such devices continued to be sold till the twentieth century, when they gradually fell into disuse in England, being replaced with the more durable rubber condoms.

References in Literature

The specimens recently discovered are very similar to that described by Casanova (1725–98) in his *Mémoires* (Paris, 1931–2 ed., vol. 5, p. 275), where he speaks of a "petit habit d'une pellicule transparente d'environ huit pouces, sans issue et armée à son entrée d'une faveur rose passée dans une coulisse." Similarly, elsewhere, he writes of being shut up "dans un morceau de peau de mort pour avoir le bonheur de vous prouver que je suis parfaitement en vie."

In England these sheaths were often praised in the poetry of the period, and in Joseph Gay's *The Petticoat* (1716) we read that

> "The *New Machine* a sure Defense shall prove,
> And guard the sex against the Harm of Love."

and that in this great invention there can be discerned what can only be called "Master-strokes of Art." Again in *The Potent Ally* (1741), as in the more famous *Panegirick upon Cundums*, it is said that

> "Happy the man, who in his pocket keeps,
> Whether with *Green* or *Scarlet* Ribbon bound,
> A well made C——M."

the same article being described in *A New Description of Merryland* as "proper cloathing, of which they have a sort that is very commodious." It was, it is stated, made "of an extraordinary fine thin substance, and contrived so as to be all of one Piece, and without a Seam, only about the Bottom it is generally bound round with a scarlet ribbon for Ornament." Similar praise is to be found in *The Machine* (1744), where a plate depicts the making of the "capotes anglaises," and where, for the sake of safety, two are advised to be worn.

In London the chief purveyors of these goods were Mrs. Philips, Mrs. Perkins, and Mrs. Lewis, of whom Mrs. Philips was the best known and widely recognized not only in England but also in France, where her goods were called "les plus renommées," as we can see from a passage in Andréa de Nerciat's *Le Diable au Corps*. In colloquial speech these sheaths were often called *armour* in England, and thus we find in Boswell's accounts of his adventures in London and Holland occasional mention of these articles when he is narrating some of his amorous engagements in "armour complete."

It is, however, in the *Panegirick upon Cundums* above mentioned that we find the most laudatory verses "in Cundum's mighty Praise." These pieces of "intervening Armor" permitted

> "Joys untasted but for them,
> Unknown Big Belly and the squawling Brat."

and are also said to be the best guard of modesty, while in that "soft answer to a scurrilous satyr," *Almonds for Parrots*, the inventor of these sheaths is styled the "Patron of the Paphian Deity."

Prevention of Venereal Disease

Medical views of these early contraceptives were strongly influenced by the use to which they could be put as a preservative against venereal disease. Fallopius, as is well known, discussed an early form of sheath; and Hercules Saxonia in his *Luis Venereae perfectissimus tractatus* (1597) described a similar device made of some kind of linen soaked in a solution and allowed to dry, a method actually hinted at by the notorious eighteenth-century writer John Marten, who refrained from giving details of the wash lest it should give "too much encouragement to the Lewd." Later authors also did not approve of these sheaths for various reasons, principally, it would seem, because they allowed libertines occasionally to escape the results of their illicit connexions. Thus, for example, Gervais Ucay, writing towards the end of the eighteenth century, although aware of these mechanical methods, maintained that the best preservative was continence. Daniel Turner (1667–1741) regarded the suggestion of Fallopius as being given with "greater Vivacity than Veracity," while Joseph Cam went so far as to say that these methods of preventing venereal disease "ought not to be allowed in a Christian Country," since to advise mankind to "use Machinery, and to fight in Armour" was merely to propagate wickedness. On the other hand, E. C. Bourru stated in 1770 that these English sheaths were subject to tears, and as they were "criblée d'une infinité de pores" they were of little use as a preventive of disease and were, moreover, invented for the purposes of libertinism.

E. J. DINGWALL.

Correspondence

Because of the present high cost of producing the Journal, and the great pressure on our space, correspondents are asked to keep their letters short.

Research into Familial Intestinal Polyposis

SIR,—For more than 25 years the research department of St. Mark's Hospital, assisted by an annual grant from the British Empire Cancer Campaign, has been collecting information about the inheritance, pathology, and treatment of familial intestinal polyposis (*Polyposis intestini*).

More than 50 families have been investigated, and in each case a complete family pedigree has been constructed. A special follow-up department has been organized to keep in touch with all these polyposis cases and their relatives, of whom more than 1,000 are now included in the hospital records. It would be of great assistance to the further development of this work if doctors who know of other cases of generalized intestinal polyposis would be good enough to send me the names and clinical details of such patients, having obtained their permission to do so. This would enable me to trace linkages between new cases and families already investigated. If any such linkage could be discovered, either now or at a later date, I should inform the doctor at once, but should not of course communicate with the patient unless the doctor wished me to do so.

I am signing this letter because I am responsible for organizing this research, but I should like it to be understood that all the surgical staff of St. Mark's Hospital are actively co-operating in this investigation.—I am, etc.,

The Research Department,
St. Mark's Hospital, City Road,
London, E.C.1. CUTHBERT DUKES.

Kwashiorkor

SIR,—Dr. Charles Rotman's proposals (December 6, 1952, p. 1257) for nutritional research into the treatment of kwashiorkor reveal considerable misconceptions concerning the metabolism of proteins. Dr. Rotman implies that kwashiorkor cannot be adequately treated with a vegetable protein diet because vegetable proteins are little used by our intestinal organisms for growth and synthesis of vitamins. In the first place, the only protein available to the bacteria is the undigested part of the diet. This is usually greater on vegetable diets than on animal foods because of the mechanical occlusion of the digestive enzymes by the indigestible cellulose. Secondly, the limiting factor in intestinal bacterial nutrition would appear to be carbohydrate rather than amino-acids, because poorly digested carbohydrate, such as uncooked potato starch, permits rapid growth of intestinal bacteria. Thirdly, Dean showed (October 11, 1952, p. 791) that vegetable protein can cure kwashiorkor.

Dr. Rotman's admiration of the adaptability of the human body because it can manufacture its own protein (we presume that the phrase "its own vitamin" in his letter is a *lapsus linguae*) is very naive. The human body can manufacture proteins only from their constituents, the amino-acids, which are present in a wide variety of proteins ranging from sows' ears to silk. The body simply takes from the dietary protein such amino-acids as it requires to synthesize protein, and oxidizes the rest. The trouble arises when some of the required amino-acids are absent from the ingested proteins. The required amino-acids are frequently as well supplied by vegetable proteins as by animal. For example, five common vegetable proteins, wheat bran, potato tuberin, soya bean, rice and maize germ, all have biological values for the rat of about 75, while four common animal proteins, casein, pork, gelatin, and blood, have biological values of only 69, 74, 25, and 16 respectively. Dean's findings are in

agreement with the theory that vegetable proteins can be as useful as animal proteins, particularly if consumed in adequate amounts.

Dr. Rotman's final suggestion of modifying the intestinal flora to deal with larger quantities of vegetable protein is unnecessary, because we already deal fairly well with vegetable protein. If, however, the implication is that we could then deal like ruminants with the vegetable cellulose, we suggest that it would take more than succinylsulphathiazole to convert man into a cow.—We are, etc.,

A. E. BENDER.
London, N.W.10. D. S. MILLER.

Abscess in Femoral Hernial Sac

SIR,—Dr. J. S. Mehta's report (November 29, p. 1203) of a case of "Abscess in Femoral Hernial Sac" interested me because on November 21, 1952, I operated on a patient for strangulated femoral hernia and found that the hernial sac contained the appendix.

A woman aged 63 was admitted to hospital with a history of vague colicky umbilical pain and nausea of seven hours' duration. A small lump over the right femoral ring had been present for a year or two, but had never been painful until the onset of the present symptoms. Before the hernial sac was opened the presence of the tip of the appendix was diagnosed by palpation. Some difficulty was experienced in entering the sac because of adhesions, and when the appendix was cleared and the canal dilated it was apparent that the appendix was under considerable tension. It was decided to open the abdomen through a Battle's incision. The caecum was fixed high on the lateral wall, and the appendix was stretched to the femoral canal, pulling the caecum into a funnel shape.

Fulminating inflammation of the herniated appendix would produce the condition described by Dr. Mehta.—I am, etc.,

Bridge of Earn, Perthshire. H. A. GRAHAM.

Puerperal Psychiatric Illness

SIR,—Dr. R. E. Hemphill, in his article on puerperal psychiatric illness (December 6, 1952, p. 1232), has drawn attention once again to the importance of this grave complication of child-bearing. Does he imagine, however, that it is possible to undertake a serious psychiatric study of 37,000 patients? Even to obtain the barest information from the case notes over the period in question would be more than a major undertaking. But, this apart, maternity hospital clinical records would not as a rule draw attention to psychiatric abnormalities in the patient's medical history or of the family history. Nor can a psychiatric study even begin to be of any value without a clinical examination of each patient by a psychiatrist, preferably whilst the patient is still under observation in hospital.

It is therefore not possible, as he suggests, adequately to explore "physical and psychological factors" under the conditions imposed in his survey. Nor is it correct to refer to the investigation as "a psychiatric study of 37,000 women delivered in maternity hospitals." Surely the method of "sampling" on a smaller number of maternity hospital patients would have given results of greater value?—I am, etc.,

Warwick C. TETLOW.

Ageing of Cartilage

SIR,—We have read with interest Dr. B. F. Matthews's findings (December 13, 1952, p. 1295) of the relationship between function and the collagen/chondroitin sulphate ratio of human articular cartilage. For the last two years we have been investigating the aetiology and pathogenesis of osteoarthritis of the hip-joint, and in the course of this work we have studied, with the help of Dr. F. Schajowicz, the histochemistry of the articular cartilage therein. At present we are engaged upon a quantitative confirmation of the qualitative results so obtained. We feel that we must draw attention to our own findings, as they have some bearing on the problem of cartilage ageing discussed by Dr. Matthews.

We have worked only with the hip, an ideal joint in which to differentiate between weight-bearing and non-weight-bearing areas, and have found, like Dr. Matthews, the highest content of muco-polysaccharide in the cartilage of those areas which are exposed to maximum stress. However, contrary to his supposition, these surfaces do not show particular "susceptibility to degeneration," but usually retain their healthy appearance. A full report of our work is now being prepared for publication.—We are, etc.,

J. TRUETA.
Oxford. M. H. M. HARRISON.

Erythema Nodosum

SIR,—My attention has been drawn to the paper by Drs. Lasar Dunner and R. Hermon (November 15, 1952, p. 1078) on "Erythema Nodosum with Bilateral Hilar Gland Enlargement." These authors refer to a previous paper by me,[1] and state: "Middlemiss (1949), reporting on 124 cases, found 56 with pulmonary changes, only one of which bears any possible relationship to ours. He regards his case as non-tuberculous, although the Mantoux reaction was strongly positive at 1:10,000."

The relevant extracts from my paper are: "Cases of similar nature have been observed by Bonnet (1946) and Kerley (1942), and most observers are agreed in not regarding them as a manifestation of tuberculosis. . . . It is, however, interesting to note that in this case the Mantoux reaction was very strongly positive." And later: ". . . Over the age of 15 . . . a positive (Mantoux) reaction has been useful in that, not being negative, it did not exclude tuberculosis as a possible aetiological factor. Such cases, therefore, have been regarded as *possibly* tuberculous in origin."

The reference to my paper appears to me to be misleading.—I am, etc.,

Bristol, 2. J. H. MIDDLEMISS.

REFERENCE

1 *Brit. J. Radiol.*, 1949, **22**, 375.

Self-demand Feeding

SIR,—May an ordinary family doctor let a little common sense in before these "feed-on-demand" extremists make a worse mess of things than ever the regular-hours fanatics did?

Nearly all mothers have got to shop, do their housework, etc., and very many of them demand a certain amount of personal freedom as well. An average baby adapts itself rapidly to, and thrives on, regular feeding. Most of us learned to compromise with the clock a fair amount for the first weeks, particularly as regards giving one night feed; and took the "regular hours" advice as strictly as we could without causing a lot of screaming. We got on very well, and it is not easy to believe that we did physical or psychological harm. Of course those doctors, nurses, and mothers who insisted unimaginatively on precise regular hours from birth had a horrid time in a proportion of cases. They deserved to.

Now this new-old idea is threatening to be at least equally harmful. Only an excessively motherly mother who drops or neglects everything else entirely can manage "feed-on-demand" as it stands in our highly organized and conventional society. The sensible mother will compromise with the new rules and regulations just as her mother did. But those who lack judgment and are particularly anxious to do just as they are told (and how numerous they are) need protection from the zeal of these enthusiasts. Incidentally the profession, as a profession, should protect itself against an accusation of detachment from reality. Surely we can keep near the middle of the road, interested in, but not too much influenced by, the antics of our "innovators."

May I say, in conclusion, how much I enjoyed the excellent article of Dr. J. D. Hay *et al.* (November 29, 1952, p. 1180). It is not their activities, as such, that worry me, but their reinterpretation by average unthinking people blindly following the fashion.—I am, etc.,

Woodford Green, Essex. E. B. GROGONO.

Routine Dental Treatment

SIR,—There has been considerable correspondence recently in both the national and the professional press about the advisability of training dental nurses to perform dental operations.

It is pathetic to see day after day in the dental department of a large general hospital numbers of young children attending for the extraction of teeth which earlier treatment could have saved. It has been officially estimated that to provide adequate routine dental treatment for our population it would be necessary to double the number of practising dentists. Since this is not possible in any foreseeable future, the only alternative is to employ in the most urgent work men and women trained to carry out specified forms of treatment under supervision—the "ancillaries" to whom the British Dental Association is so strongly opposed.

I have recently been examining a class of dental hygienists for their Ministry of Health certificate, and have, as on previous occasions, been struck by their keenness, their grasp of the necessary anatomy and physiology, and the manual dexterity which they have attained after only one year's training. First-hand experience of their work in various hospitals reinforces my conviction that in a second year nearly all of them could be brought to a point at which they could do simple fillings and extract deciduous teeth quite as well as the great majority of dentists. It is in my opinion much to be hoped that the reintroduction and enactment of the Dentists Bill, which lapsed upon the recent prorogation of Parliament, will enable this important experiment to be made with the least possible delay.—I am, etc.,

Birmingham RALPH A. BRODERICK.

Vaccination Technique

SIR,—May I support Dr. Harry G. Jeffs (December 6, p. 1256) in his condemnation of the present practice of leaving vaccination sites uncovered? During an outbreak of smallpox early in 1951, 11 children were seen who had secondarily inoculated their own right eyes simply by rubbing them with contaminated fingers. The pustules were at the same stage of development as the primary inoculations on the left arm. Some apprehension was felt that trichiasis might ensue, as it was predominantly the lash follicles that were involved. This complication did not in fact occur in any of the cases seen, but two children had corneal involvement, one superficial, the other deep.

Apart from hazard to the eyes, these instances served to prejudice many of the general public against the practice of vaccination, and could, one felt, have been avoided by the application and maintenance of a dressing.—I am, etc.,

London, W.8. W. IDA PEARCE.

Abuse of Antibiotics

SIR,—Mr. Norman C. Lake's letter (December 13, 1952, p. 1807) on this subject is healthily disturbing. As it illustrates a real danger in the use of antibiotics, I would like to record the brief outline of a minor surgical case I saw.

An otherwise fit young labourer abrased the volar pad of a finger. Four days later he noticed the signs of inflammation. One week after sustaining this trivial injury he first came to the casualty department. On examination there was a well-developed subcutaneous infection, localized to the distal phalangeal area. There was no evidence of any distal pulp involvement. Besides local treatment and an injection of A.T.S., a course of 900,000 u. distaquaine penicillin was ordered, to be given twice daily. The patient's temperature was taken and recorded at each visit. Initially this was 98.6° F. (37° C.); subsequently it showed no fall, but had risen to 99.4° F. (37.4° C.) at the sixth visit. The local condition remained apparently unchanged during these three days.

Early detection of the penicillin-resistant nature of the infecting organism was thus made. Routine employment of this measure allowed for the timely use of alternative treatment. The penicillin was stopped immediately. Aureomycin in 0.5-g. doses was given, six-hourly, instead. Within 24 hours the condition of the finger showed definite improvement and the temperature had returned to normal.

Without temperature readings at each attendance, there would have been much less chance of avoiding complications. There would have been virtually no barrier raised to the possible development of cellulitis, distal pulp, or even tendon sheath infections.—I am, etc.,

London, N.1. DUNCAN D. MACDONALD.

SIR,—Mr. N. C. Lake's warning (December 13, 1952, p. 1307) on the use and action of the sulphonamides and antibiotics is indeed opportune, and there is no field of surgery in which his words are more applicable than in that of otolaryngology. I think that it was in acute middle-ear infections that the masking effect of sulphonamides was first noted with some apprehension.

It is incontestable that in otology an unwise or inadequate use of this therapy has resulted in catastrophe, and cases could be recorded, if space would allow, which illustrate how a patient has been lost, or the onset of an intracranial involvement has supervened, directly as a result of failure to recognize that the initial otitic invasion has been masked. Masking can so completely abolish the classical signs and symptoms upon which we perhaps too readily depend for guidance that the aural infection may appear, at all events to the unwary, to be dead, until an unexpected meningitis or more fortunately a protruding mastoid swelling has revealed that something has been missed. A belated examination of the drumhead and hearing, corroborated by radiography of the mastoid, has then indicated that in spite of the absence of the common signs and symptoms, and in spite of the improved condition and well-being so frequently accompanying the use of the therapy, the truth has been that the middle-ear and mastoid cavities have been full of pus for some weeks.

These troubles generally arise from a disregard of the basic surgical principle that pus, wherever accessible, requires drainage, and the tendency in some quarters to-day to substitute these agents in place of surgery should be strongly resisted. This therapy can be used very early after the onset of acute otitis media with safety and benefit, but it must be accompanied by repeated examinations of the ear-drum and hearing in order to see that resolution is taking place. In acute suppurative otitis media, a later and more virulent stage, it should be withheld until after myringotomy and bacteriological testing for sensitivity. The distortion in pathological processes which can result from this therapy renders the exudate more sticky, the membrane more oedematous, and yet the tension within the tympanum is lowered: thus the drum is less likely to rupture spontaneously or to drain so efficiently.

Sulphonamides, owing to their bacteriostatic action, may do little more than inhibit or discourage the infection, whereas the antibiotics by their bactericidal powers may slay it outright, but both, if they fall short of the powers within them through incorrect administration, may so distort the clinical picture and pathological processes as to make them unrecognizable. On the other hand, the achievements of these therapeutic agents have been immense, particularly in the case of the antibiotics. They can be used with benefit in sensitive cases in any stage of acute otitic infection or complication, such as mastoiditis, sinus thrombosis, meningitis, or brain abscess, so long as all necessary surgery has been carried out, and so long as there is no obscurity about the diagnosis of the lesion or any extension therefrom. If there is any doubt about the completion of these two essential factors, the therapy must be withheld. Recovery from pyogenic otitic meningitis was really unknown until the advent of these agents; to-day it is almost a commonplace. When used at the correct time and stage of

infection, they have been one of the most prominent factors in causing the acute mastoid operation to be the rarity that it is to-day. As a prophylactic and cover against infection in major operations on the larynx and pharynx they are essential, and have reduced the mortality rate in laryngectomy from a depressingly high figure to a negligible one. No surgeon to-day would be wise to undertake such operations without their assistance.

One aspect of the action of antibiotics which I think is not sufficiently realized is their ability to forestall infection of certain organs and tissues. It is impossible to say how many ears and nasal sinuses have escaped infection, particularly in the acute specific fevers, as a result of their attack on the nasopharyngeal infection, but it is certainly a very large number. By their beneficial effect on the blood-stream infection they must frequently prevent pulmonary and renal involvement. They thus provide a prophylaxis against extension of infection hitherto unknown. By doing so much for the patient, however, they induce him to become lazy in his own interests, with the result that efficient immunity is not built up as it would be if the infection had been fought unaided; this may explain the frequent recurrences, often over a short interval, noted in acute otitis media, suggesting that complete recovery from the first attack had never taken place.

Mr. Lake is doing a service in emphasizing how grossly this therapy is over-prescribed and in urging his plea that it be reserved for severe infective illness or as a cover in suitable major surgical cases.—I am, etc.,

London, W.1. A. R. DINGLEY.

The College of General Practitioners

SIR,—For many general practitioners Christmas will be brighter this year than any since the war, and this not only because some of us have larger bank balances this December than for many years past. It can have been no accident that the announcement of the completion of the spadework by the Steering Committee was made before the New Year but after "Danckwerts." So let us all respond to the good news of the birth of the new College by joining at once as foundation members, by paying our joining subscription promptly, and—one more thing—making a gift to the College of a substantial amount of money to raise a Foundation Endowment Fund.

Money is power, and we all want the new College to be powerful for our good. Money given now is more valuable than money given in six months' or a year's time. Money given by members of the profession who are not general practitioners will be an especial encouragement to the College, and it would be into such an Endowment Fund that these donations could best be paid. I have to-day sent a cheque for what is to me "a substantial amount of money" to the Secretary of the new College asking him to pay it into or use it to start such a Foundation Endowment Fund, and I appeal to every member of the profession to consider whether he can also do this as a birthday present to the new College.—I am, etc.,

Peaslake, Surrey. G. I. WATSON.

SIR,—With the passing of the National Health Service Act general practice entered upon an entirely new phase. For the first time the majority of general practitioners began to work under broadly the same conditions. This fact was bound to lead ultimately to a realization of the need for greater co-ordination and co-operation between practitioners. Here, at last, is the means to that end. The Report of the General Practice Steering Committee (1952) (*Journal*, December 20, 1952, p. 1321) offers a hope for the future which is sorely needed.

Although only a recent entrant into the field, I have been closely connected with general practice all my life, and I can fully realize the potentialities of the College of General Practitioners. The foundation of the college will be looked upon as a triumphal step forward, and as deserving of the fullest support.

I venture to suggest that it is in the initiation and co-ordination of research that the first concrete results will be produced. The scope is enormous; unfortunately, however, those who desire to undertake research frequently find time a limiting, and sometimes crippling, factor. The help and guidance of the college will, I trust, imbue all general practitioners with renewed vigour and enable much important work to be carried out.—I am, etc.,

Stoke-on-Trent. H. W. K. ACHESON.

Specialists in Physical Medicine

SIR,—Your correspondents (December 13, 1952, p. 1307, and December 20, 1952, p. 1358) replying to my comments (November 29, 1952, p. 1203) on Lord Horder's letter (November 15, 1952, p. 1095) all agree that there is extravagance in the prescription of courses of physiotherapeutic treatment. They are likewise of one mind in advocating the appointment of more consultants in the subject as a remedy for this state of affairs. They may be right, but I venture to think that the problem is more complex than such a simple solution suggests.

One factor tending to crowd departments is the conception in the mind of many members of the community that their every ache and pain should justify a course of therapy—preferably one of an "ultra" electrical character. Another is the habit, mentioned by Dr. Alan Stoddard, of some practitioners—both general and special—to use physical medicine departments as a dump for their less responsive patients. I cannot help feeling that the solution of the problem would be eased if these practitioners recognized their own responsibility in the matter and attempted to educate the public to an attitude of greater self-help in dealing with minor conditions.

Mr. Harold Balme's letter (December 27, 1952, p. 1417), which I have just read, is mainly concerned with the important subject of rehabilitation of the disabled. My comments have been related to the management of *minor* injuries and ailments. To make my point of view clear to him, I would say that in some departments of physical medicine in the metropolitan regions overlong or unnecessary courses of physiotherapy are too often prescribed for relatively trivial conditions. This results in the overcrowding of departments and thereby handicaps their effective conduct. It also more often than not prolongs convalescence and encourages an attitude of dependence on the patient's side. The provision of more consultants in physical medicine will not prove an adequate remedy for this state of affairs.

The question of what course of study and experience is calculated to produce good consultants in physical medicine is a controversial one. In a specialized therapeutic technique, the successful practice of which is often as dependent on psychical influence as on the actual physical method employed, the desirable qualifications of the consultant are difficult to define. I would, however, suggest that possession of the current diploma in the subject is no more than an annexe to the wide clinical experience which is desirable.—I am, etc.,

Faversham, Kent. MAX PAGE.

The Patient's Story

SIR,—It was, to speak moderately, somewhat disturbing to read the leading article "The Patient Tells His Story" (December 6, p. 1246), in which we were told of history-taking (albeit experimental) by means of a four-page questionary—the C.M.I. In my view this is an overt crystallization of a tendency to an attitude of mind that has been growing amongst many medical men in recent years; an attitude which eschews too much critical thought and blurs the outline of mental concepts; and, further (and perhaps more important), relegates the patient to the category of a quasi-Descartian structure.

Unfortunately the tone of the leading article was apparently favourable to this new method. "It is yet another form to be filled in," it runs, "but it raises no objection in the patient's mind, for it obviously advances his own interest. . . ." That a questionary of 195 questions is another "form" would appear an evident truth even to the dull-witted, but whether the patient would regard it in the light of positively advancing his own interests appears much less evident. Again, the four-page dossier "precedes the personal history-taking." It might appear that if

history-taking is personal there would be little need for the answers to 195 form questions; or, if the form is used, that there should be small necessity for interrogation.

The original three papers on the C.M.I.[1] contain numerous case reports demonstrating its powers. A fairly representative case is that of a woman who complained of "shooting pains in both ears," and, "without questioning her about other symptoms, the admitting physician referred her to the ear, nose, and throat department. . . ." Interpreters of her C.M.I. form (independently covering the same period) stated that she required care for "disorders of her eyes, ears, respiratory tract, blood pressure, cardiovascular system, urinary tract, teeth, gall-bladder, skin, gynaecological endocrine system, weight, veins of the lower extremities and emotional disorders." Subsequent investigation revealed systemic hypertension with cardiac failure, and disorders due to the effects of obesity, the menopause, varicose veins, and an anxiety state. This catalogue dazzles not so much with the perspicacity of the seemingly almost electronic-brained C.M.I., but rather with the doctor's apparent unwillingness to utilize a little time and relatively elementary cerebration. It is also, in passing, a commentary on the obverse side of this coin—namely, over-specialization.

Medicine has been described as both art and science, and the doctor employs the methods of the historian on the one hand and the natural scientist on the other. But this is an oversimplification, and to historical method must be added the entity of personal contact of doctor and patient. Medicine, in this sense, is an amalgam of art and science in symbiotic well-being. If this concept, which has been most fully and admirably discussed by Walshe in the Linacre Lecture for 1950, is true, then to depart from it is to strike a mortal blow to such symbiotic eunomy. "Every physician," says Walshe, "and especially every teacher of medicine, knows that what is called 'history-taking' is a task calling for experience and critical thinking, and that it cannot be learned with the ease to which the techniques of clinical examination often lend themselves. This is in accord with . . . the nature of historical evidence, and of its criticism, selection, and assembly in the writing of history: a complex intellectual exercise in which the evidence is given *life and meaning* by the historian's own contribution of thought and knowledge." I have italicized "life and meaning" because this is also given by face-to-face contact with the patient, a point which is adequately brought out by Byrom Bramwell in an address to students (*Studies in Clinical Medicine*, 1889): "By following this part of the examination, you will learn the method of conducting the oral examination, and will get valuable hints as to the different modes of eliciting information and of dealing with patients of different temperaments."

Surely, then, in applying the "historico-personal" method of examination (if I may so call it) the aim is to be confronted by the patient when you question him and for him to be confronted by you; for the emphasis is not upon invoking and arranging a past (as you might an archaeological past) but a *personal* past. Only then may the examiner's question be framed in the light of the answers given to previous questions already asked—*while in the presence of the patient.* Only then will he observe the emotional and bodily response to both question and answer. Interpretation of meaning is notoriously difficult at the best of times, so that interpretation of even so simple a question as "Are you breathless?" is open to error which I cannot see avoided by the patient encircling either "Yes" or "No" on a form: on the contrary, the magnitude of error, I would forecast, is likely to be increased.

In another field of knowledge Professor Tawney has remarked that social workers must go to the core of social problems—as in discovering how people live by living and talking with them—"to test the validity of those hidden springs (of life) which answers to a questionary cannot and do not reveal." I hope my confrères of the younger generation will critically examine and reject any harbinger of decay in the intellectual, practical, and humanistic approach to medicine.—I am, etc.,

London, S.W.3. RAYMOND PARKES.

REFERENCE

[1] Brodman, K., Erdmann, A. J., jun., Lorge, I., and Wolff, H. G., *J. Amer. med. Ass.*, 1949, **140**, 530; 1951, **145**, 152; and 1952, **149**, 550.

B.C.G.

SIR,—Dr. H. G. Calwell's letter (December 6, p. 1256) has caught the eye of the anonymous physician who took part in the broadcast on tuberculosis in children. The reply to the question, "Will B.C.G. prevent tuberculous meningitis?" was not, "No, I don't think so," but, "Yes, I believe it will"; the "No" answer was in reply to a question asking if there was a cure for tuberculosis. (This answer has been checked with the B.B.C.). It was indeed in the belief that this is a true statement that the reply was made, and Dr. Calwell will doubtless agree that the figures from the speaker's B.C.G. vaccination clinic records in no way tend to upset his belief.

Up to date, 3,400 infants have been successfully vaccinated and no cases of tuberculous meningitis or deaths from tuberculosis have occurred, whereas in non-vaccinated infants and children in the chief city of the region there have been, during the same period of time, 26 deaths from tuberculous meningitis.—I am, etc.,

"ANONYMOUS PHYSICIAN."

POINTS FROM LETTERS

Two Matters for Thought

Dr. G. C. PETHER (Hitchin) writes: Two matters have interested me and may justify investigation. It is suggested that some of the effect of liquid paraffin, used as a laxative, is due to the presence of traces of ring compounds. I believe these may be carcinogenic. Is it not possible that lung cancer has sometimes been caused by these substances when inhaled from nasal sprays, as distinct from the more common pneumonic process? The importance of fluorine in the development of healthy teeth is admitted. Before steel rollers were used in grinding flour, stones were used. Some of these, such as the French burr stone, contained fluorides which would mix with the flour in a finely divided form favouring assimilation. If this is so then steel rollers may not represent an advance in preparing our bread. Some years ago a miller worked out for me the amount of stone dust in a sack of flour, but I have mislaid the figures.

Measles

Dr. W. H. REES (Swanage) writes: Your annotation on measles (November 29, p. 1196) seems to stress the treatment of bronchopneumonia and otitis media after these conditions have become established. I believe that most cases of pneumonia and otitis media in measles can be prevented by the routine use of a sulphonamide in all cases of measles. Sulphadimidine is useful for this purpose and it is much easier to give to children than injections of penicillin. It is my belief that sulphadimidine reduces the secondary bacterial invasion of not only the lungs and middle ear but the whole respiratory tract. In consequence the duration of nasopharyngitis, cough, malaise, and pyrexia is shortened in all cases in which it is used.

The Law and Homosexuality

Dr. ELLIS STUNGO (London, W.1) writes: I recently attended assizes to give medical evidence for the defence in the cases of two men, aged respectively 26 and 21, charged with homosexual offences. They were first offenders of good character in other respects, with excellent Army and employment records. The older man was an only son and the sole support of his invalid mother and crippled father. He was sentenced to 15 months' imprisonment. The other, at adjacent assizes, was bound over on the condition that he became a voluntary patient at a mental hospital for a period of six months. Their offences had been committed in private. There had been no question of importuning or corrupting young persons. Both men had readily admitted their guilt when questioned by the police, who had obtained their names as a result of inquiries into the activities of others. It is lamentable in my view that the first case should have been sent to prison, possibly to share a cell with one or more hardened criminals. . . . Could anything be more conducive to the encouragement of unnatural practices than confining men for long periods in an overcrowded prison? The condition of residence in a mental hospital in the case of the other offender could serve no useful purpose other than to render him more available for such therapeutic sessions as the already overworked medical staff could provide. . . . My object in writing to you is not to press for any alteration in the law relating to homosexual offences, which is nevertheless desirable, but to suggest that official medical experts should be available in court to advise judges on the medical aspects, if any, of these cases. I feel sure that they would welcome such an innovation, which would also preclude medical testimony being available only to those who could raise the necessary funds. It would also avoid the irritation of their lordships occasioned by the optimistic prognostications of overzealous psychotherapists, whose evidence is so often unceremoniously but wisely ignored.

Obituary

CHARLES PORTER, M.D., M.R.C.P.Ed.

We record with regret the death in London of Dr. Charles Porter on December 15, 1952, at the age of 77.

Charles Porter was born at Edinburgh on June 19, 1873, the second son of Mr. Alexander Porter, and was educated at the Royal High School, Edinburgh, and at the Universities of Edinburgh and Freiburg. He graduated M.B., C.M. at Edinburgh in 1896 and proceeded M.D., with high commendation, in 1902. He was elected M.R.C.P.Ed. in 1902, and two years later he took the Edinburgh B.Sc. in public health, winning the Parkin Prize of the Royal College of Physicians of Edinburgh in the same year. From 1902 to 1906 he was lecturer on bacteriology in the University of Sheffield. After holding public health appointments at Leeds and Finsbury, he became medical officer of health for St. Marylebone in 1910, a position he held until his retirement in 1939. He returned from his retirement in October, 1945, to become acting medical officer of health for Paddington and continued in that capacity until November, 1946.

During nearly 30 years in Marylebone Dr. Porter was closely concerned with the formulation and supervision of many schemes undertaken by the council for the improvement of the health conditions of the people of the borough, especially in connexion with slum clearance, housing, and maternity and child welfare services, several of which were the first of their kind under municipal schemes. His activities, however, were not restricted to local public health matters. He was president of the Society of Medical Officers of Health in 1933–4 and chairman of the council of the Royal Sanitary Institute in 1931–3, a body of which he was also vice-president. He served upon many Departmental Committees and, at the invitation of the Minister of Health, took part in international health conferences in other countries. He was an Honorary Fellow of the American Public Health Association, and among other bodies of which he was for many years a member were the General Nursing Council for England and Wales, the council of the Queen's Institute of District Nursing, the Royal Sanitary Institute, the Sanitary Inspectors' Examination Joint Board, and the Worshipful Company of Plumbers, whose Master he was for the current year. Dr. Porter had been lecturer on public health at the Middlesex Hospital Medical School and the London School of Hygiene and Tropical Medicine and an examiner for the D.P.H. of the Conjoint Board and for the B.A. (Architecture) of the University of London, and was a member of the Board of Studies in Hygiene of the University. When the British Medical Association held its Annual Meeting in Belfast in 1909 he acted as one of the secretaries of the Section of Hygiene and Public Medicine. Well known as a writer on matters concerning public health and preventive medicine, Dr. Porter was for 10 years the honorary editor of *Public Health*, the official organ of the Society of Medical Officers of Health. Apart from works on many different aspects of hygiene, he was joint author of a standard textbook on sanitary law.

Dr. Porter, whose kindliness, wit, and charm endeared him to so many people in St. Marylebone and beyond, remained energetic and deeply interested in all matters of health, hygiene, and sanitation until the end. He leaves a widow, Mrs. Geraldine Porter, and a son and three daughters by a former marriage. A memorial service will be held at St. Marylebone Parish Church on Friday, January 9, at 12.15 p.m.

Dr. H. A. BULMAN, who succeeded Dr. Porter as medical officer of health of St. Marylebone, writes as follows: Charles Porter, with his short, stocky, monocled figure and inexhaustible energy, was indeed a great personality. An outstanding authority on preventive medicine, his reputation and influence extended far beyond St. Marylebone, which he served as medical officer of health with such distinction for nearly 30 years. He took a foremost part in grappling with the many public health problems of his day and inevitably was to be found in the midst of controversies ranging over a wide field, from epidemiological research to the severely practical and revolutionary "one-pipe" system of drainage for buildings.

He had a keen journalistic sense and was a prolific writer—indeed, his only hobbies were reading and writing. Apart from being author, editor, commentator, and reviewer, he contributed a weekly page to a public health journal for many years, never missing an issue even though he might be in America for three or four months taking part in an international health officers' course or reporting abroad to a world health organization. Most of his work was set in type from his own neat handwriting, and he had an uncanny knack of writing just sufficient to fill the space allotted to him.

In addition to his work for D.P.H. students, he was keenly interested in the training of sanitary inspectors and health visitors, and his name was a household word to a host of those officers who studied under him and eventually found him a lively, sympathetic, but searching examiner.

He excelled as an after-dinner speaker and was greatly sought after for the aptness of his comments and the brilliance of his wit. Charles Porter did not suffer fools gladly, but for those prepared to work hard with him he was an inspiring and fearless leader and a delightful and helpful friend.

F. N. REYNOLDS, F.R.C.S.Ed., F.R.C.O.G.

Mr. F. N. Reynolds, well known for his advocacy of improved methods of relieving pain in childbirth, died in London on December 22, aged 57.

Frank Neon Reynolds was born on June 11, 1895, and educated at Epsom College and St. Thomas's Hospital Medical School. He qualified in 1917, but by this time he had already seen war service at the Dardanelles, and he was later to be present at the Battle of Jutland and at the blocking of Ostend as a surgeon lieutenant R.N. After the war he returned to St. Thomas's, where he became chief assistant in the obstetric and gynaecological departments. Then followed a series of appointments at the Hospital for Sick Children, Great Ormond Street. It was after this that Reynolds finally decided on a career of obstetrics and gynaecology, and in 1925 he was appointed to the post of registrar and pathologist to the Hospital for Women, Soho Square—a position he held until 1928. It was during this period that Reynolds worked with the late Sir Henry Simpson, at that time surgeon to the Hospital for Women, Soho Square, modelling himself on Sir Henry and acquiring much of that great and lovable obstetrician's technique and mental approach to midwifery.

From 1929 to 1930 Reynolds was associated with Mr. Hedley as his assistant in the obstetric and gynaecological departments of St. Thomas's Hospital, and then

followed many appointments, including those of consulting surgeon to the Hospital for Women and Children, Harrow Road, consulting gynaecologist to the Hackney Borough Council, gynaecologist to the Southend General Hospital, and examiner to the Central Midwives Board.

He gained the F.R.C.S.Ed. in 1925, and was elected F.R.C.O.G. in 1942. When in that year Sir Eardley Holland gave up his position as consulting gynaecologist to the County of Hertfordshire, Reynolds became his successor. The duties of this post in wartime were very arduous, and Reynolds was responsible for the work of 12 emergency maternity homes under the evacuation scheme of the Ministry of Health. He was consultant in obstetrics to the general practitioners of Hertfordshire as well as to the maternity units of the voluntary and municipal hospitals of the county, and he was also gynaecologist to the Wellhouse Hospital, Barnet. In 1947 he was appointed surgeon to the Hospital for Women, Soho Square, an appointment which gave him great happiness because of his earlier work and associations. He held this appointment with great distinction until his death.

In his capacity as consultant obstetrician to the Hertfordshire County Council Reynolds was able to put into action plans which he had devised for improving the work of midwives, particularly in connexion with analgesia in childbirth. This was a subject always close to his heart, and in fact he spoke on it at one of the Plenary Sessions at the Annual Meeting of the B.M.A. in Dublin last year, where he was a vice-president of the Section of Obstetrics and Gynaecology. He contributed several papers to this and other journals on obstetrical subjects, and his book *Relief of Pain in Childbirth* was published in 1934.

Frank Reynolds will always be remembered by his colleagues and intimate friends as a man of exceptional charm and character. He was essentially a tolerant, kindly, sympathetic man, with charming manners and a sense of medical etiquette and propriety rather rare in these days. His tact and consideration for others endeared him to the nursing and administrative staffs with which he worked, and his modesty, kindliness, and unselfishness made him equally beloved by his colleagues.

He married Freda, younger daughter of Mr. A. R. Wilson, in 1926, and he is survived by his widow, one son, and two daughters.

ROBERT JAMES PROBYN-WILLIAMS, M.D., F.F.A.

Dr. Probyn-Williams, who was the first to hold the post of anaesthetist to the London Hospital, died on December 14 at the age of 86, at Wotton-under-Edge, Gloucestershire.

Robert James Probyn-Williams was born on May 19, 1866. He received his medical education at the University of Durham and the London Hospital, graduating M.B., B.S. in 1889, and taking the Conjoint diploma the following year. He proceeded M.D. in 1892. After holding house appointments at the London Hospital he was appointed anaesthetist there in 1896, retiring from the post of consultant anaesthetist in 1926. Among his other posts were those of lecturer in anaesthetics to the London School of Clinical Medicine, Greenwich, and anaesthetist to the Royal Dental Hospital. In the first world war he served in the R.A.M.C. in the 2nd London General Hospital. The author of a number of papers on anaesthesia, he also published two books, *A Practical Guide to the Administration of Anaesthetics* (1901) and *Golden Rules of Anaesthesia* (1904). He served as president of the Society of Anaesthetists in 1906, which later became a section of the Royal Society of Medicine.

We are indebted to Sir HUGH LETT for the following personal appreciation:

The death of Dr. R. J. Probyn-Williams severs a link between the anaesthesia of to-day and that of the closing years of the last century, for he was appointed anaesthetist to the London Hospital in 1896. At that time the science of anaesthesia was comparatively rudimentary. Clover's inhaler for ether, the celluloid mask and sponge for A.C.E., the flannel-covered frame and perhaps a Junker's inhaler for chloroform, a gag and a few dental props and a pair of tongue forceps with a sponge or two, were practically all the anaesthetist required apart from the anaesthetics themselves. Gas was given for dental extractions and very brief minor operations, but the combination of gas and oxygen was still to come.

Surgery was still limited in its scope, although the number of operations, especially those on the abdomen, was steadily increasing, but the arrangements for anaesthetizing patients were far from satisfactory. In 1896 Frederick Hewitt, later Sir Frederick, was the only anaesthetist at the London Hospital, and he had been appointed not as an anaesthetist but as instructor in anaesthetics. It was clearly necessary that surgeons should be provided with experienced anaesthetists on their regular operating days and not have to rely on the doubtful services of their house-surgeons or other residents. Accordingly the post of anaesthetist to the hospital was instituted. Probyn-Williams was the first to be appointed, and within three years two further appointments were made. These and similar appointments at other hospitals gave anaesthetists the status of members of the visiting staff, led to an increase in their number, and emphasized the growing importance of the subject. This period may perhaps be considered a landmark in the history of anaesthesia.

Probyn-Williams, popularly known as Probang, was much interested in the students. He always turned out for the staff in the annual golf match against them and seldom missed a rugger cup-tie when the London was playing. His kindly, courteous, unhurried manner endeared him to the many who passed through his hands during the 30 years he worked at the hospital. Music and photography were among his interests, but Masonry was pre-eminent. He attained the high rank of Past Grand Deacon and was a founder of the London Hospital Lodge and for many years its secretary. A few months ago he came up from the West of England to attend the fiftieth anniversary of its consecration. He was then 86, but he made light of the journey, and those who had not seen him since he left the hospital 26 years before saw little change in his appearance. He made an admirable speech and received a warm welcome. The news of his death will be received with deep regret by all who knew him.

J. HENDERSON SMITH, M.B., Ch.B.

Dr. John Henderson Smith, who died on November 26, 1952, at the age of 77, had a career that covered an unusual range of interests and activities. After graduating in classics from Balliol College, Oxford, in 1898, he read medicine at Edinburgh, where he took the degrees of M.B., Ch.B. in 1903. A return to Oxford, during which he held the Philip Walker Studentship in pathology, was followed by periods at medical laboratories in Copenhagen, Dresden, and Freiberg. In 1907 he was appointed to the Lister Institute for Medical Research, where he continued his work on bacteriology and immunology. This research was interrupted by illness in 1913, but he was able to return for some wartime work in producing diagnostic sera. In 1916 his health again broke down and, to his bitter disappoint-

ment, he was forced to give up his work at the Lister. Three years' convalescence found him able to resume work but not to return to town life, and he accepted an appointment in the newly formed department of mycology at the Rothamsted Experimental Station, Harpenden. His first work in plant pathology was a valuable study of the killing of fungus spores by heat and phenol, and he also contributed to knowledge on the manner in which fungal hyphae grow. His main interest, however, passed to virus diseases of plants, a subject then little studied in Great Britain. In 1929 his leadership in the field was recognized by the establishment, with funds provided by the Empire Marketing Board, of a team of three to study the properties of viruses under his direction. Progress was rapid, and the next ten years saw a complete change in views about these pathogens. His own studies, in conjunction with Miss Sheffield, were mainly on the formation of intracellular inclusion bodies and on the estimation of particle sizes by filtration. He became head of the department in 1933, when its name was changed to Department of Plant Pathology, and held the post until he retired in 1940.

Henderson Smith had a keen analytical brain. That, combined with his forthright speech and clear writing, made him a merciless critic of bad work or unwarranted conclusions, but he was also objective and willing to accept novel concepts when the evidence was good. His presidential addresses to the Association of Applied Biologists in 1938 and to the Virus Section of the Microbiological Congress in 1939 showed that he was one of the first of those trained as a bacteriologist to appreciate the significance of the biochemical work on plant viruses done in the 1930's.

He was an enthusiastic golfer and—a more unusual hobby—a collector of book-plates, of which his knowledge was immense. It was his intention in retirement to record this knowledge in a book, but, regrettably, he did not do so. Perhaps, as with much of his scientific work, it remained unpublished because he set himself standards too exacting to be achieved.—F.C.B.

F. C. EVE, M.D., F.R.C.P.

We are indebted to Dr. PETER C. MCKINLAY for the following appreciation of the late Dr. F. C. Eve, whose obituary notice was published in the *Journal* of December 20, 1952 (p. 1362): By the death of Dr. F. C. Eve, British medicine has lost a figure known the world over for his work on artificial respiration. He first conceived the rocking method when he applied it to a Hull child apparently dying of diphtheritic paralysis of the diaphragm, and the parents co-operated to save the child's life by continuous see-saw movements in a rocking-chair for two days. To his scientific outlook he added a knowledge of mechanics, and in 1937 he evolved a tiltable bed which was first used in the Hull Children's Hospital. It was at his suggestion that Hull Royal Infirmary became the first general hospital to build, in 1903, open-air balconies for beds. He took an early interest in clinical psychology when it was not fashionable, and, though he never accepted the full claims of modern psychological medicine, his interest in the reactions of body and mind remained to the end. He had many interests outside his profession and was a keen golfer, tennis player, and trout-fisher, and he won a silver medal for figure-skating. His lifelong interest in birds and trees found fresh avenues when his home in Hull was "blitzed" in 1941 and he came to live in Beverley. He had several years of intermittent chronic ill-health, but from his bed he made many observations on Nature; in this field he was a mine of surprising information. Shortly before his death he was preparing a small book on the life of rooks, concluding from his observations that their communal life was similar to man's, but much better organized. His bed was usually strewn with papers, latterly recording his ideas of theories of energy, on which he hoped to publish a book. The proposed title, "Attractions Prevail—Separations Diminish," embodied his ideas, which sought to harmonize the divergent views of nuclear physicists and metaphysicians. Its acceptance by either group would have been dubious, but one privileged to attend him professionally could not but be impressed by the fertility of his mind, ever receptive to new ideas which he would pursue far into the by-ways of speculation. To visit him was a mental exercise, made all the more pleasant by his unfailing courtesy, courage, and quiet sense of humour.

The death occurred at Edinburgh on September 12, 1952, of Dr. RACHEL ELIZABETH WOODMAN MACKENZIE, the eldest daughter of the late Rev. J. S. Mackenzie, of Little Dunkeld, Perthshire. Born in 1869, Dr. Mackenzie received her professional training at the London School of Medicine for Women, and graduated M.B. of the University of London in 1896. After graduation she went to India as a medical missionary for the Church of Scotland at Sialkot, in the Punjab. Health reasons obliged her to return to this country after six years' service in India, and she entered private practice at Walthamstow, in London. She took the Oxford D.P.H. in 1910, and in 1918 was appointed assistant medical officer of health at Woolwich, where she was the first medical officer appointed for maternity and child welfare in the borough. The successful development of the scheme was due largely to her efforts.—W. H. H.

Dr. ALBERT FREDERICK LEOPOLD SHIELDS, who died at Weybridge on November 26, 1952, was born in Ireland in 1890, and was educated at Queen's University, Belfast, where he graduated M.B., B.Ch. in 1914. He entered the R.A.M.C. immediately after qualifying, and served throughout the war of 1914–18, attaining the rank of major. At the end of the war he decided to study ophthalmology, and in the years between the two world wars practised in London as an ophthalmic surgeon. In 1939, in which year he took the D.O.M.S., Colonel Shields, who was on the R.A.M.C. Reserve of Officers, was recalled for service and went to France in September, 1939, as ophthalmic surgeon to No. 7 General Hospital with the rank of lieutenant-colonel. He returned to England after the evacuation of France in 1940, and was in turn in command of No. 4 Casualty Clearing Station, Winchester, and the Military Hospital, Shrewsbury, and chairman of the medical board which dealt with cases to be referred to St. Dunstan's at Church Stretton, Shropshire. Shortly afterwards he was attacked by arthritis, and was invalided out of the Army in 1943, when he resumed his appointment as clinical assistant to the Royal Westminster Ophthalmic Hospital. The London hospitals at that time were very short of clinical assistants, and Shields was soon engaged also at the Royal Eye Hospital and in the ophthalmic department at St. Thomas's Hospital, his assistance at both hospitals being much appreciated. By 1944 he had obtained the posts of ophthalmic surgeon to St. John's Hospital, Wandsworth, and Queen Mary's Hospital for Children, Carshalton, and to the Brentford and Teddington school clinics, appointments which he held until the time of his death. Dr. Shields was a delightful character, full of fun and good fellowship and always ready to help his patients and colleagues. A man with the kindest of hearts, he seldom lost his temper, and when he did he lost it with a twinkle in his eye so that the outburst never

offended. He had a most infectious laugh and a keen sense of humour. He will be mourned by a large circle of friends as well as by his patients. He leaves a widow, to whom our deep sympathy is extended.—T. M. T.

The death of Dr. M. CAMPBELL ANDREWS was recorded in the *Journal* of November 22 (p. 1157). J. S. R. has sent this appreciation: Campbell Andrews was of a rare spirit. What he gave to life—and he was always giving—was made the more valuable by a constant courage that never weakened. He was a man fearless for himself and his position, whether he was in opposition to established authority, on the unpopular side in committee, or taking grave decisions affecting a patient's life and happiness. He never feared being thought wrong or being wronged, and his only endeavour was to do that which he regarded as right. He had a profound admiration for the late Mr. Mitchiner, but never saw that he himself had in abundant measure the same honesty and generous disinterestedness that gave such a towering stature to Philip Mitchiner. Campbell Andrews died as he lived, with unblemished courage, and his compassion for the suffering of others was matched only by the fortitude and even humour with which he endured his own. He inspires us as we mourn him.

Dr. H. G. CALWELL writes: I should like to supplement your obituary notice (December 6, p. 1263) of WILLIAM KERR CONNELL, with whom I served for many years in the Colonial Medical Service in the Tanganyika Territory. Connell not only performed a large number of surgical operations under most difficult climatic conditions, mostly in a hospital whose amenities in the strict sense of that word were non-existent, but he had enough energy of mind and body left to write a handbook of surgery for the use of African medical assistants in training. The high quality of this book, in matter, illustration, and form, indicates the esteem in which he held his African pupils. On retirement from the Colonial Medical Service Connell returned to anatomy, and was appointed to the chair in that subject in the Anderson College of Medicine, and later became a member of the staff of the department of anatomy in the University of Glasgow. Not many men have obtained the Fellowship of the Royal College of Surgeons of England when on leave from a single-handed bush hospital in the Tropics, and not many have become successful teachers of anatomy 25 years after their demonstrator days. Connell achieved both feats.

Medical Notes in Parliament

HOSPITAL STAFFING

Mr. A. BLENKINSOP on December 19 asked for information about a circular issued by the Ministry of Health on economy in manpower.[1] It made important and striking changes in the staffing of hospitals and would embitter the relationship between the hospital management committees and regional hospital boards. The circular provided for a comprehensive review of hospital staff, but in addition it provided that there had to be an immediate return of existing staffs of all hospitals and a freezing at a wholly arbitrary figure.

By the operation of this circular hospital management committees were being stripped of some of the last vestiges of their authority. He asked whether the Ministry was in process of disbanding the hospital management committees. Matters which had been within the competence of management committees would now be transferred to regional hospital boards, and matters within the competence of the boards would be referred for decision by the Ministry. Why had the Ministry given up the view taken as recently as February, 1952, that proper establishment should be agreed upon and should be made compulsory, if necessary subject to review by a higher authority? What criteria would the Minister use in deciding whether additional staff were to be approved or not?

[1] See *Supplement*, p. 2.

Getting Staff Where Needed

Replying, Miss PATRICIA HORNSBY-SMITH said the planned programme for dealing with staffing of the hospital service had been going on for some time. It was essential that progress should be made in view of the disparity, in some cases wide, between the staffing of hospitals. The circular would help to get the staff where they were most needed. It merely specified that there should be no overall increase in establishments within a group. There were shortages in some areas, and in other areas ample evidence had been obtained that in some hospitals there had been overstaffing. The principle of establishing staffs and placing authority on the regional board and the Minister for their appointments had been accepted throughout the hospital service since its institution. The Minister had made it plain that where there were shortages he intended that permission should be given for those shortages to be made up.

The Select Committee on Estimates had recommended in July that staffing of hospitals should be reviewed on a national basis by the Ministry of Health, and that the individual hospital board should be given more extensive powers of controlling the size of the staffs of hospital management committees than it possessed at present. That view was accepted. It had been confirmed by the Central Health Services Council. The memorandum recently issued by the Minister had been referred to the Committee of Regional Hospital Board Chairmen. These held a special meeting to discuss it, and in the course of that meeting consulted Ministry officials. They had ironed out points of detail and agreed to operate the scheme.

Reorganization of Duties

The memorandum required hospital boards and hospital management committees to obtain prior consent of the next highest authority before they increased their staff. In many institutions that had been in operation for some time. There had been remarkable successes in reorganization of duties. in putting in more equipment and labour-saving devices. and in discontinuance of unessential work. Regional hospital boards would share in the reviews of the hospital management committees.

This memorandum did not propose any target for the reduction of any medical or nursing staffs, nor did it impose control over individual appointments. Vacancies would be filled as an ordinary matter of routine. Only increases in total number of staffs had to be justified. Most of the staff was employed by some 400 hospital management committees receiving authority from regional hospital boards. When one realized that 65% of the £225m. spent on the hospital services alone went in salaries and wages of hospital staffs, it was absurd to think of any review of the finance of the National Health Service if this vast field of expenditure was to be ignored. So far as manpower was concerned, in 1951 there were 15% more full-time staff and 33% more part-time staff than in 1948. The Ministry must be satisfied that there was no waste of national manpower. Purely financial control of the budget was not enough. The Minister's responsibility was to see that both the manpower and the finance of the National Health Service were conducted with the greatest care and prudence.

Antibiotics for Animals.—The Government intends, if the results of current trials are confirmed, to introduce legislation to permit the use of antibiotics in animal feeding under suitable safeguards. The necessary Bill is in preparation.

INFECTIOUS DISEASES AND VITAL STATISTICS

Summary for British Isles for week ending **December 13** (No. 50) and corresponding week 1951.

Figures of *cases* are for the countries shown and London administrative county. Figures of *deaths* and *births* are for the 160 great towns in England and Wales (London included), London administrative county, the 17 principal towns in Scotland, the 10 principal towns in Northern Ireland, and the 14 principal towns in Eire.

A blank space denotes disease not notifiable or no return available.

The table is based on information supplied by the Registrars-General of England and Wales, Scotland, N. Ireland, and Eire, the Ministry of Health and Local Government of N. Ireland, and the Department of Health of Eire.

CASES in Countries and London	1952					1951				
	Eng. & Wales	Lond.	Scot.	N. Ire.	Eire	Eng. & Wales	Lond.	Scot.	N. Ire.	Eire
Diphtheria	23	3	7	1	1	42	2	12	1	4
Dysentery	328	10	75	2	2	337	43	39	1	2
Encephalitis, acute	10	1	0	0		7	1	0	0	1
Enteric fever:										
Typhoid	1	0	1	0	6	1	0	0	0	0
Paratyphoid	4	1	2(B)	0	0	17	0	7(B)	0	
Food-poisoning	74	11		1		55	13		0	
Infective enteritis or diarrhoea under 2 years				13	13				13	18
Measles*	17,742	1404	241	27	113	2,448	16	139	179	98
Meningococcal infection	39	4	13	2	2	29	3	14	2	4
Ophthalmia neonatorum	32	1	7	0		37	3	5	0	1
Pneumonia†	1,135	131	472	8	1	583	30	183	9	
Poliomyelitis, acute:										
Paralytic	41	1	2	3	2	36	1	8	0	3
Non-paralytic	17	2				8	0			
Puerperal fever‡	233	35	16	1	1	226	35	5	0	1
Scarlet fever	2,229	131	302	34	70	1,543	131	312	31	44
Tuberculosis:										
Respiratory			133	22				136	30	
Non-respiratory			24	5				29	5	
Whooping-cough	1,865	75	129	21	122	1,929	51	324	57	88

DEATHS in Great Towns	1952					1951				
	Eng. & Wales	Lond.	Scot.	N. Ire.	Eire	Eng. & Wales	Lond.	Scot.	N. Ire.	Eire
Diphtheria	1	0	0	0	0	*0*	0	*0*	0	0
Dysentery	1	0		0			0		0	
Encephalitis, acute		0			0		0			0
Enteric fever	0	0	0	0		*1*	0	*0*	0	
Infective enteritis or diarrhoea under 2 years	10	2	3	1	0	*5*		*3*	0	3
Influenza	60	24	4	1	1	*17*	3	*2*	0	0
Measles		0	0	0	0		0	*0*	0	1
Meningococcal infection		1	2				0	*2*		
Pneumonia	597	168		8	16	*192*	33		8	6
Poliomyelitis, acute	4	1			0	*2*	0			0
Scarlet fever		0	0	0	0		0	*0*	0	0
Tuberculosis:										
Respiratory	259	77	31	3	7	*151*	22	*21*	5	7
Non-respiratory		5	1	0	2		2	*1*	1	1
Whooping-cough	6	0	0	0	0	*3*	0	*0*	0	0
Deaths 0–1 year	295	54	49	18	18	*230*	33	*25*	10	15
Deaths (excluding stillbirths)	9,452	2484	861	143	224	*5,119*	855	*600*	122	154
LIVE BIRTHS	7,157	1050	854	211	342	*6,161*	1000	*768*	187	328
STILLBIRTHS	202	22	26			*167*	26	*20*		

* Measles not notifiable in Scotland, whence returns are approximate.
† Includes primary and influenzal pneumonia.
‡ Includes puerperal pyrexia.

Vital Statistics

Deaths in the Fog

During the five days December 5 to 9, 1952, the greater part of Metropolitan London was enveloped by smoke-laden fog, and there was a spectacular rise in deaths registered in Greater London during the week ending December 13. The total was 4,703—more than double that for the preceding two weeks (1,902 and 2,062 respectively), and more than treble that for the corresponding period in 1951. Deaths due to "influenza" and pneumonia showed a comparable rise from 89 in the week ending December 6 to 380 in the week of the fog. Remarkable too was the number of deaths from respiratory or cardiac disease referred to the coroners in London. The increase varied from twice to five times the expected seasonal number of necropsies.

Informal reports from a variety of sources suggest that the duration and density of the smoke-laden fog could largely explain the dramatic increase in deaths from respiratory and cardiac disease in the middle-aged and elderly.

A study of the meteorological conditions in London at the time shows that high barometric pressure, low ground temperature, and high relative humidity continued for the five days of the fog. Elsewhere in southern England similar observations were recorded, not necessarily accompanied by fog. Preliminary reports of the chemical analysis of the fog show that there was an increase in sulphur dioxide and in carbon content.

A number of investigations are now in progress; they include a detailed analysis of the deaths by age and cause as stated on the death certificate, examination of the reports of pathologists, a study of lung chemistry in certain fatal cases, and further chemical study of the fog and smoke.

London's Health in 1951

The Report for 1951 of Dr. J. A. Scott, County Medical Officer to London County Council, shows that the infant mortality rate fell again to a new low level of 25.4 per 1,000 live births. The general death rate of 12.6 per 1,000 population was higher than the previous year (11.3), probably owing to the influenza epidemic and the continued ageing of the population. The birth rate fell slightly, to 15.6 from 15.7, though it remains well above the pre-war level. The neonatal death rate rose from 16.9 to 17.3 per 1,000 live births, but the 1950 figure was the lowest on record in London. The average for the past 10 years was 20.4.

The report draws attention to a steady decline since 1949 in the number of children receiving primary immunization against diphtheria. About 41,000 were immunized for the first time, as against 47,000 in 1950. The decline is attributed to two causes: first, exaggerated reports of cases of paralytic poliomyelitis following inoculation, and, secondly, apathy due to the low incidence of diphtheria. The numbers of vaccinations and revaccinations increased, about 35,000 vaccinations being performed in 1951, and about 28,000 in 1950.

The number of home confinements attended by the Council's midwives has continued to decline; there were 7,040 in 1951, while there were nearly 13,000 in 1947. The decline is due partly to the falling birth rate and partly to the greater availability of hospital beds. An inquiry into premature babies born at home showed that, of 219 nursed at home, 199 were entirely breast-fed when the case was discharged by the midwife.

Road accidents caused 282 deaths, compared with 245 in 1950. The report points out that each year a heavier toll is taken by the roads than by any poliomyelitis outbreak so far experienced.

Fewer verminous children were found at school inspections than in previous years: 0.1% of boys and 0.2% of

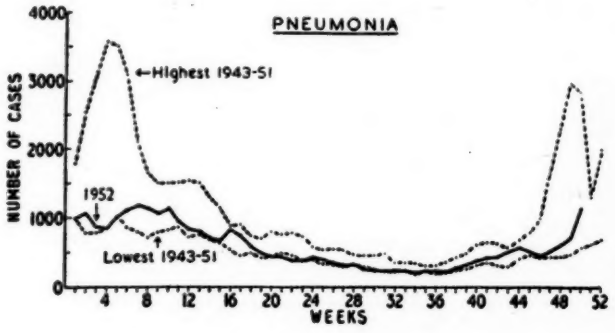
girls were found to have hair lice in 1951, as compared with 0.3% and 0.9% in 1948.

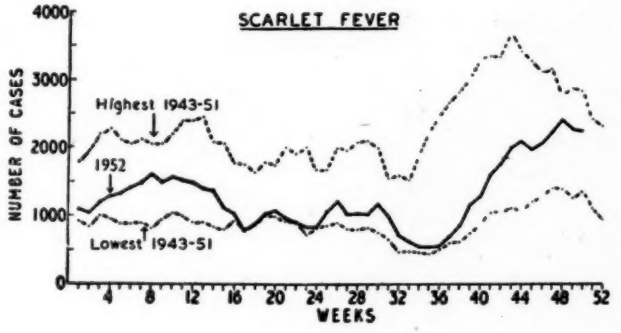
Road Accidents in November

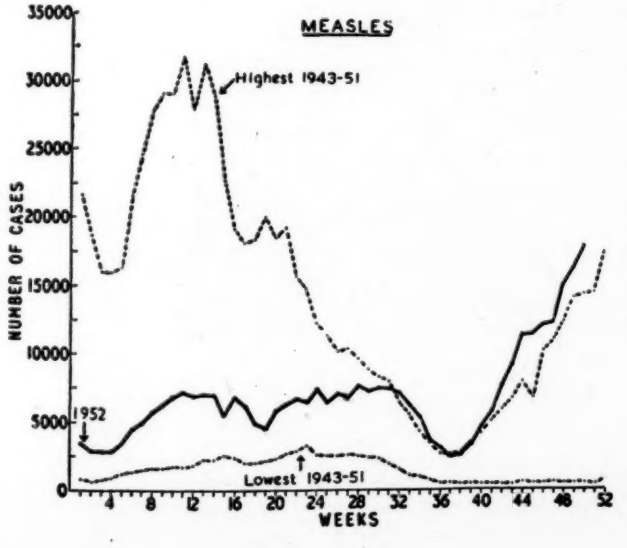
Road casualties in November totalled 16,259. This includes 412 killed and 4,186 seriously injured. Compared with November, 1951, the total figure is less by 2,793, and the numbers of killed and seriously injured by 151 and 662. A few reports are probably still outstanding.

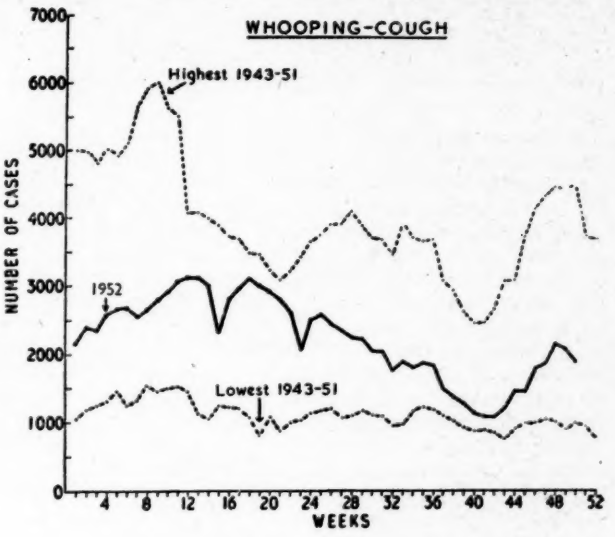
Graphs of Infectious Diseases

The graphs below show the uncorrected numbers of cases of certain diseases notified weekly in England and Wales. Highest and lowest figures reported in each week during the nine years 1943–51 are shown thus - - - - - -, the figures for 1952 thus ————. Except for the curves showing notifications in 1952, the graphs were prepared at the Department of Medical Statistics and Epidemiology, London School of Hygiene and Tropical Medicine.









Infectious Diseases

The largest rises in the incidence of infectious diseases in England and Wales during the week ending December 13 were 1,535 for measles, from 16,207 to 17,742, and 416 for acute pneumonia, from 719 to 1,135, while the only large fall was 202 for whooping-cough, from 2,067 to 1,865.

The largest increases in the number of notifications of measles were Lancashire 289, from 1,268 to 1,557, Warwickshire 294, from 609 to 903, Middlesex 181, from 742 to 923, Glamorganshire 129, from 378 to 507, and Leicestershire 102, from 464 to 566. The chief exception to the rising trend of measles was a fall of 105 in Yorkshire North Riding, from 554 to 449. The number of notifications of scarlet fever was 30 less than in the preceding week; the largest local variations were a fall of 40 in London, from 171 to 131, and a rise of 57 in Yorkshire West Riding, from 218 to 275. The only large variation in the local trends of whooping-cough was a fall of 59 in Lancashire, from 367 to 308. 23 cases of diphtheria were notified, 6 fewer than in the preceding week. The largest centres of diphtheria were Plymouth C.B. 4 and Liverpool C.B. 4.

An increase in the incidence of pneumonia was general throughout the country. The largest rises were 78 in Lancashire, from 82 to 160, and 70 in London, from 61 to 131. A large rise also occurred in the mortality from pneumonia during the week; the number of deaths in the great towns rose from 303 in the preceding week to 597.

The notifications of acute poliomyelitis were 7 fewer for paralytic and 7 more for non-paralytic cases than in the preceding week. The largest returns were Sussex 5, Kent 4, Middlesex 4, Essex 4, and Norfolk 4 (Wayland R.D. 3).

The rise in the incidence of dysentery was due to an increase in two outbreaks; these were Leicester C.B., where the cases rose from 21 to 52, and Grimsby C.B., with a rise from 15 to 35. The other large returns were Yorkshire West Riding 68 (Rothwell U.D. 36, Nidderdale R.D. 15), Lancashire 50 (Liverpool C.B. 12, Bolton C.B. 11, Blackpool C.B. 10), Kent 30 (Penge U.D. 25).

60 deaths, 32 more than in the preceding week, were attributed to influenza in the great towns.

Week Ending December 20

The notifications of infectious diseases in England and Wales during the week included: scarlet fever 1,881, whooping-cough 1,748, diphtheria 23, measles 19,551, acute poliomyelitis 47, dysentery 327, paratyphoid fever 1, and typhoid fever 5.

Medical News

A Journal Centenary.—On Friday, January 7, 1853, was published in London the first issue of the *Association Medical Journal*, which four years later was to become the *British Medical Journal*. The *Association Medical Journal* appeared weekly, and was the direct continuation, under a new title, of the *Provincial Medical and Surgical Journal*, which had been in existence since 1840, being published at first weekly but later fortnightly from Worcester, the home of the Provincial Medical and Surgical Association. But much more important for the future of the journal than the change of title were its move to London and the decision to place it under a single editor. As Dr. Cowan, the main instigator of the changes, pointed out at the Association's annual meeting at Oxford in 1852, to continue publishing from Worcester would only perpetuate provincial weakness and defects, but in London an editor would possess great advantages from his central position—a view fully shared by Dr. Cormack, the chosen editor of the newly named journal.

Experiments on Human Beings.—On Christmas Eve, after a trial before a French military tribunal at Metz lasting nine days, two German doctors, Dr. Otto Bickenbach and Dr. Eugen Haagen, were sentenced to hard labour for life. They were being tried for experiments carried out during the war at the Struthof concentration camp in Alsace. Bickenbach was accused of murdering gipsies in a gas chamber during experiments on poisonous gases. Haagen was charged with using prisoners for testing an anti-typhus vaccine. Both doctors pleaded mistaken identity, and are appealing against their sentences.

Life Assurance and Medical Research.—Following American precedent the Life Offices' Association of Australasia has established a fund for the promotion of medical research in Australia and New Zealand. According to the current issue of the *Medical Journal of Australia* it is expected that a sum of about £25,000 will be disbursed annually. As a start the fund will be used to support work on cardiovascular diseases, as these are the commonest causes of death in Australia and New Zealand. Grants will be made either as grants-in-aid to institutions or as research fellowships. The latter will be tenable both in Australia and New Zealand and abroad. A distinguished group of medical scientists, under the chairmanship of Dr. S. A. Smith, has been appointed to advise on the application of the fund's resources. The medical director of the fund is Dr. J. H. Halliday. The creation of the fund is warmly welcomed in a leading article in the *Medical Journal of Australia*.

Fellowships in Clinical Research.—The Medical Research Council invites applications for Fellowships in Clinical Research, tenable at centres in the United Kingdom during the academic year 1953–4. These Fellowships are open to suitably qualified medical graduates who desire to prepare themselves for a career in clinical research. In general, it is intended that each Fellow appointed under the scheme should be given an opportunity, as part of his training for clinical research, to study methods of research in the basic subject most germane to his particular clinical interest. The awards will be made for a period of one year in the first instance and will be renewable annually in approved cases up to a maximum of three years in all. Stipend will be at the rate of £850 per annum, rising by annual increments of £75 to £1,000 per annum, and in addition superannuation provision will be made (or continued within the National Health Service Scheme, if applicable, by arrangement with the Ministry of Health and the Department of Health for Scotland). Candidates for these Fellowships must be medically qualified and clinically experienced, and should preferably have worked for a period in a department in which clinical research was in progress. Applicants will be invited to submit their own proposals as to type and place of work, but the Council will be glad to advise successful candidates on the selection of suitable centres of study and to assist in placing them in departments or laboratories where the desired training and experience can be obtained. Applications must be sponsored in each case by the head of the appropriate department in the candidate's university or medical school, and an undertaking will be required that a suitable academic post in a clinical department will be available to the candidate in that institution on satisfactory completion of the period of study under the Fellowship. Forms of application for these Fellowships may be obtained from the Secretary, Medical Research Council, 38, Old Queen Street, London, S.W.1, with whom applications should be lodged as soon as possible, and in any event not later than March 1.

Consumption of Milk.—In reply to questions on the effect of price increases on the consumption of milk in this country, Dr. Charles Hill, Parliamentary Secretary to the Ministry of Food, was able to give some reassuring figures last month. During the first 11 months of last year there was a fall of only 1.6% in the total sales of liquid milk compared with the same period in 1951. Consumption of full-price milk fell off by 1.9%, but there was also a 1% fall in the consumption of school milk, which had suffered no price increase. These declines, however, must be set against the steadily rising trend of liquid milk consumption during the previous 14 years. In 1938 860 million gallons were consumed in the United Kingdom, while in 1951 the figure was 1,574 million gallons.

Hepatitis and Blood Transfusion.—Regional blood transfusion centres are now turning down all donors with a history of infective hepatitis, however long ago the attack occurred. The reason for this is that recent American work suggests that in some individuals the causative virus may linger in the blood stream for many years after apparent clinical cure. It is considered unlikely that this decision will make it necessary to recruit a large number of extra donors.

Methorphinan Scheduled.—By an Order in Council made on December 4, 1952, and which came into force on December 8, the dextro, laevo, and racemic forms of 3-methoxy-N-methylmorphinan have been scheduled under the Dangerous Drugs Act, 1951. The Order applies to all the salts and to "any preparation, admixture, extract, or other substance containing any proportion" of the drug. Methorphinan ("dromoran") is an analgesic which closely resembles morphine in structure (see *British Medical Journal*, December 20, 1952, page 1328).

Family Doctor.—The January issue of *Family Doctor* is now out. It contains articles by two professors as well as by other medical men. Professor W. C. W. Nixon, with two colleagues, writes on "Having a Baby," and Professor R. S. Illingworth on the child who won't go to sleep. A medical psychologist, Dr. John Brandon, discusses memory, while another psychologist, this time a laywoman, writes about old age. Strictly medical subjects, on which family doctors must be prepared to answer patients' questions, include sciatica and the surgery of the heart. In addition there are a lay version of "Any Questions?" called "Expert Advice," a page on marriage problems, and a thoughtful discussion of the patient's dilemma of when to call the doctor. The medical dish is served up with a savoury sauce of light general articles and items that will appeal especially to the mother and housewife. *Family Doctor* costs 1s. 6d., and is widely available from newsagents and booksellers.

Bequests.—Dr. Colin Gordon, of St. Saviour, Jersey, left the residue of his estate, after payment of certain annuities, to the University of Edinburgh for the foundation of research scholarships in medicine or science to be known as the "Colin Gordon and Ethel Gordon Scholarships."

Emergency Bed Service: Applications and Admissions.—During the seven days ending December 29 the number of applications made by doctors to the London Emergency Bed Service for admission of patients was 1,379, of whom 93.03% were admitted.

Dr. J. A. Hadfield, lecturer in psychopathology and mental hygiene at London University, delivered the presidential address to the Conference of Educational Associations at King's College, London, on December 29. He spoke about religion as a force for moral behaviour.

Dr. Macdonald Critchley, dean of the Institute of Neurology, has been elected corresponding foreign member of the Académie de Médecine of France.

NEW ISSUES

Annals of the Rheumatic Diseases.—The next issue (Vol. 11, No. 4) will be available in a week's time. The contents include:

EFFECTS OF A.C.T.H. AND CORTISONE ON THE ANAEMIA OF RHEUMATOID ARTHRITIS. J. O. P. Edgcumbe and O. A. N. Hussain.
LA POLYARTHRITE MASCULINE. J. Forestier and F. Jacqueline.
CLINICAL INVESTIGATION OF THE VALUE OF SYNTHETIC HYALURONIDASE INHIBITORS IN RHEUMATOID ARTHRITIS. L. Hahn, S. Thune, and E. Truedsson.
VALUE OF INTRA-ARTICULAR INJECTIONS IN OSTEO-ARTHRITIS. M. H. L. Desmarais.
COLLAGENOUS PSEUDOTUMOURS OF THE HANDS. Otto C. Kestler.
OSTEOPHYTOSIS OF THE LUMBAR SPINE. O. D. Beresford.
BLOOD GLUTATHIONE LEVELS IN RHEUMATOID ARTHRITIS. D. Watson, D. S. Bidmead, and G. D. Kersley.

Issued quarterly; annual subscription £2 2s.; single copy 12s. 6d.; obtainable from the Publishing Manager, B.M.A. House, Tavistock Square, London, W.C.1.

SOCIETIES AND LECTURES

Details in this column are necessarily brief. Further information and tickets where required (marked ●) should be obtained from the institution concerned.

Monday, January 5

ROYAL EYE HOSPITAL.—5 p.m., Dr. T. H. Whittington: Convergence, Heterophoria. Introduction to Orthoptics.

Tuesday, January 6

BRITISH POSTGRADUATE MEDICAL FEDERATION.—At London School of Hygiene and Tropical Medicine, 5.30 p.m., Sir James Spence: Methodology of Clinical Science.
●INSTITUTE OF DERMATOLOGY.—5.30 p.m., Dr. H. Haber: Cutaneous Manifestations of Syphilis and their Differential Diagnoses.

Wednesday, January 7

●INSTITUTE OF DERMATOLOGY.—5.30 p.m., Dr. J. O. Oliver: Serological Diagnosis of Syphilis.

Thursday, January 8

ALFRED ADLER MEDICAL SOCIETY.—At 11, Chandos Street, W., 8 p.m., Dr. J. D. Wyndham Pearce: Juvenile Delinquency.
BRITISH POSTGRADUATE MEDICAL FEDERATION.—At London School of Hygiene and Tropical Medicine, 5.30 p.m., Dr. S. J. Folley, F.R.S.: Pituitary Hormones in Reproduction and Lactation.
●INSTITUTE OF CHILD HEALTH.—5 p.m., Dr. C. Worster-Drought: Speech Disorders in Children of School Age.
●INSTITUTE OF DERMATOLOGY.—5.30 p.m., Dr. H. Haber: Erythema Elevatum Diutinum, Granuloma Annulare, and Allied Conditions.
LIVERPOOL MEDICAL INSTITUTION.—8 p.m., Mr. J. C. McFarland: Diagnosis and Treatment of Diseases of the Pharynx and Larynx. Also short film.
ROYAL EYE HOSPITAL.—5 p.m., Dr. S. Nevin: Diagnosis of Cerebral Tumour.

Friday, January 9

●INSTITUTE OF DERMATOLOGY.—5.30 p.m., Dr. B. Russell: clinical demonstration.
ROYAL EYE HOSPITAL.—5.30 p.m., Mr. Howard Reed: Visual Fields.
SOCIETY OF CHEMICAL INDUSTRY: FINE CHEMICALS GROUP.—At London School of Hygiene and Tropical Medicine, W.C., 7 p.m., Professor E. R. H. Jones, D.Sc., F.R.S.: New Routes to Cortisone.

BIRTHS, MARRIAGES, AND DEATHS

BIRTHS

Borrie.—On October 18, 1952, at Dunedin, New Zealand, to Helen, wife of John Borrie, F.R.C.S., a son.
Ellis.—On December 28, 1952, at Newcastle General Hospital, to Alysoun (formerly Benson), wife of Dr. Errington Ellis, a daughter.
Tucker.—On December 22, 1952, at the West Middlesex Hospital, Isleworth, Middlesex, to Helen (formerly Rennie), wife of Dr. Hugh M. Tucker, Urquhart Villa, Lossiemouth, Moray, a daughter—Gillian Helen.
Wraith.—On December 11, 1952, at the Princess Beatrice Hospital, London, S.W., to Joyce Eileen (formerly Wyatt), wife of D. G. Wraith, M.D., M.R.C.P., of London, N.W., a brother for Elizabeth Joy—Robert Francis.

MARRIAGES

Taylor—Reynolds.—On December 13, 1952, at Elm Road Baptist Church, Beckenham, Kent, Alan Richard Taylor, M.B., B.S., to Mary Gladys Reynolds, B.A.

DEATHS

Carlyle.—On December 4, 1952, at the Thomas Hope Hospital, Langholm, Dumfriesshire, Peter Murray Carlyle, M.B., C.M., of Milnholme, Langholm, formerly of Wallington, Surrey, aged 78.
Dillon-Kelly.—On December 15, 1952, at King's College Hospital, London, S.E., Cecil Francis Dillon-Kelly, M.C., L.R.C.P.&S.I. & L.M., of 15, Lancaster Avenue, West Norwood, London, S.E.
Ffrench-O'Carroll.—On December 16, 1952, in Dublin, Arthur Stevens Ffrench-O'Carroll, F.R.C.S.I., aged 56.

Any Questions?

Correspondents should give their names and addresses (not for publication) and include all relevant details in their questions, which should be typed. We publish here a selection of those questions and answers which seem to be of general interest.

Visceroptosis

Q.—*Is visceroptosis still accepted as a cause of abdominal symptoms?*

A.—The answer to this question must certainly be yes. The diagnosis of visceroptosis is probably more accurately made now than 30 years ago; the disease is a quite definite entity. The crux of the situation would seem to be a mobile caecum rather than a displaced caecum. It is possible to have both a very high and a very low caecum entirely without symptoms. But if the caecum is mobile, gravitational stasis occurs in the ascending colon and as a result the mesentery becomes a supporting structure. This leads to secondary circulatory changes (in duodenum, intestine, etc.), so that a state of chronic ileus is established leading to the well-known symptoms of distension, discomfort, constipation, flatulence, and toxic manifestations. If these symptoms are relieved by lying down—particularly after the ingestion of food—the diagnosis of visceroptosis is probably quite genuine.

Vaginal Tampons in Virgins

Q.—*Are there any strong reasons against the use of vaginal tampons by virgins during menstruation?*

A.—The reasons put forward against the use of vaginal tampons during menstruation are: (1) That their constant use may cause infection in the vagina and possibly erosion of the cervix. (2) That they are occasionally forgotten and left in the vagina for several days or weeks to produce an offensive discharge and sometimes serious pelvic infection. (3) That young virginal women often find them difficult to insert or they object to doing so. Unless the aperture in the hymen is unusually large it has to be stretched to allow the first insertion. In some girls the use of tampons may encourage masturbation or have unfavourable psychological reactions.

The first objection is largely theoretical and there is now a good deal of evidence, reviewed by Elizabeth N. Brand (*British Medical Journal*, 1952, **1**, 24), to show that the regular use of tampons does not significantly alter the vaginal flora or damage the cervix. In any case the occasional use of a tampon can do no harm. The second objection is real, so tampons should not be used except by women of reasonable intelligence who can be expected to change them frequently and to take care to avoid leaving one in the vagina. The third objection is one which applies strongly to certain women but not to others. Much depends on the mental outlook and on the anatomy of the introitus, and advice should be modified to suit different individuals.

Effect of Illness and Overwork on the Electroencephalogram

Q.—*Can external factors such as illness or prolonged mental overwork cause cerebral dysrhythmia?*

A.—The electrical rhythm of the brain waves is very responsive to changes in the internal environment—e.g., changes in the alkalinity of the blood, in the level of the blood sugar, etc. Furthermore, any lesion of the brain itself, such as an old scar from head injury, or a neoplasm, is very likely to cause one or another form of dysrhythmia. Illnesses of many kinds may therefore be responsible for cerebral dysrhythmia, but prolonged mental overwork is

not known to be among them. If a mentally overworked patient has been found to show cerebral dysrhythmia, any causal connexion between the two is likely to be intermediate—e.g., his overwork may be causing sleeplessness, fatigue, impaired appetite, inadequate attention to meals, minor hypoglycaemia at important times in the day.

Short-sighted Boxers

Q.—*What degree of myopia should be held a bar to boxing among schoolboys? Does a greater liability to retinal detachment affect the issue?*

A.—Boxing is dangerous for all myopes, even those in whom the myopia is of low degree. Liability to retinal detachment is the main reason, but it must also be remembered that myopic eyes, being more prominent than those of emmetropes, will be more often struck, so that retinal detachment is only one of many lesions which may be inflicted. Furthermore, the myope's inability to see objects in clear detail at a distance of more than a yard must preclude first-class ring technique. Therefore a myope stands all the more chance of being severely mauled in a contest.

Twitching Eyelid

Q.—*A man of 50 has been bothered for the last 18 months by a persistently twitching eyelid. What are the aetiology and treatment of this tiresome symptom?*

A.—Isolated twitching of the lower eyelid is common but seldom continues for long enough to necessitate treatment. It is more likely to develop in people who use their eyes for close work or reading, and an open-air holiday generally effects a cure. The condition is different from the much more troublesome facial spasm.

The cause is not known, but a coarse flickering of this kind suggests some defect in the conduction of that branch of the facial nerve which supplies the lower part of the orbicularis. Perhaps excessive use of the orbicularis might stretch this small nerve. I should feel inclined to experiment with various forms of treatment, but possibly the most likely to be successful would be to give a small injection of procaine directed to block the nerve going to the muscle whose fibres are twitching. If this is temporarily successful then firm massage or firm pressure over the nerve branch would have a similar slight blocking effect, and if applied repeatedly would probably give relief. The question draws attention to the need for the investigation by neurophysiological methods of this common but neglected symptom.

Pulse and Blood Pressure in the Diagnosis of Drunkenness

Q.—*In a borderline case of "drunk in charge," both pulse rate and blood pressure were at their usual levels for the patient. Does this finding contravert a diagnosis of drunkenness?*

A.—No.

The term "drunk in charge" is a misnomer, the wording of the Act being, "under the influence of drink or drug to such an extent as to be incapable of having proper control of a vehicle." A person need not, therefore, be drunk within the meaning usually attributed to the word.

No single finding can be regarded as sufficiently significant for it to be said that the accused is not contravening the Act other than the total absence of alcohol from the blood or urine, or its presence in only very low concentration. A blood pressure and pulse rate normal for the individual will therefore be of value only if the other findings at the examination are within normal limits or have an alternative explanation to being due to alcohol. Further, whereas a normal pulse rate might occur in a person under the influence of alcohol, so a tachycardia might be due to emotional disturbances, which might also account for other symptoms or signs such as tremors. The behaviour of the blood pressure must also be interpreted in a similar manner.

Prevention of Vomiting

Q.—*What is the best way of preventing vomiting when it is serving no useful purpose but just exhausting the patient?*

A.—The best way to stop vomiting is, of course, to treat the condition responsible for it. Far the most beneficial general measure is to wash out the stomach. Drugs which are used to prevent motion sickness, such as hyoscine and certain antihistamines, are sometimes effective, particularly in hyperemesis gravidarum.

Spurting Fallopian Tubes

Q.—*At laparotomy for torsion of the right Fallopian tube very early in pregnancy blood was seen to be spurting rhythmically from both tubes, in time with the heart beats. This ceased immediately the tube was untwisted. What is the explanation? The pregnancy is now proceeding uneventfully.*

A.—The result of torsion of the tube is an impairment of its circulation—the veins being obstructed first and, later, the arteries. Damage to vessels and extravasation of blood are almost inevitable, and rhythmic spurting could be explained on the basis of either that a small arteriole had ruptured or that a venous flow had pulsation transmitted to it by an underlying artery. It is not difficult to understand the occurrence on the affected side, but there is no obvious reason why the phenomenon should have been observed in the normal tube. Blood can scarcely have passed from the affected side via the uterus, otherwise abortion would almost certainly have ensued. In the absence of further details no explanation is offered.

NOTES AND COMMENTS

Garrulitas Vulvae.—Mr. E. WATSON-WILLIAMS (Bristol) has drawn our attention to an epigram by Martial (Book VII, No. 18) in which the syndrome of vaginal flatus, described recently in "Any Questions?" (November 22, 1952, p. 1164), is mentioned. Martial calls it "garrulitas cunni" and "poppysmata cunni."

Chorda Tympani and Persistent Unpleasant Taste.—Dr. A. F. MACKENZIE (Glasgow) writes: A local cause could explain such (see "Any Questions?" December 13, 1952, p. 1320). A denture of gold, or a gold clasp thereof, in contact with amalgam filling, these metals being of differing electrical potential, often produces taste of surprising intensity, sometimes with pain. A persistent focus of food-impaction fermenting also can produce the symptom.

OUR EXPERT writes: I answered the question on the understanding that there was no local lesion to account for the unpleasant taste. However, there is no doubt that patients sometimes complain of symptoms in the mouth which can be traced to galvanic action resulting from intermittent contact between metals of differing electrical potential, as suggested by Dr. Mackenzie. This state of affairs usually produces a sharp pain of short duration. It is of course possible that taste symptoms could be produced in a similar way, but I should have thought that they would be intermittent.

"Any Questions?" Book: Second Series.—This is now available, price 7s. 6d. (postage 6d. extra), from the Publishing Manager, B.M.A. House, Tavistock Square, London, W.C.1.

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